Clinical Roundtable Monograph

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Clinical Perspectives on Infliximab for the Treatment of Crohn's Disease: Considerations from the SONIC Study

Faculty

Gary R. Lichtenstein, MD
University of Pennsylvania
Philadelphia, Pennsylvania

Asher Kornbluth, MD
Mount Sinai Medical Center
New York, New York

Geert D'Haens, MD, PhD
Academic Medical Center
Amsterdam, The Netherlands

Abstract

The management of inflammatory bowel disease was revolutionized by the introduction of biologic therapies, many of which target tumor necrosis factor. Infliximab, the first of these biologic agents approved for Crohn's disease (CD), has been shown in numerous clinical studies to induce response and remission and has also been demonstrated to heal the intestinal mucosa and bring about remission without steroids. The SONIC study, which evaluated biologic- and immunomodulator-naïve patients with CD, was an important phase III trial designed to evaluate infliximab in combination with the conventional CD therapy azathioprine, an immunomodulatory agent; both agents were evaluated as single-agent treatments as well as in combination. The SONIC study demonstrated higher rates of response for infliximab-based therapy over azathioprine alone; in meeting its primary endpoint, the SONIC study showed significantly higher rates of steroid-free remission at Week 26 for patients receiving infliximab-based treatment strategies compared to azathioprine monotherapy among patients with moderately to severely active CD who had an inadequate response to conventional therapy. Now, almost 1 year following the initial publication of this study, this roundtable provides a forum in which several expert clinicians discuss its findings, including its primary and secondary efficacy endpoints. The potential impact of these findings on clinical practice is also discussed, including how these findings may impact the question of when biologic agents should be introduced into the treatment regimen for CD. Overall, the results of the SONIC study suggest that patients with moderately to severely active CD who failed conventional therapy may be managed with earlier introduction of an infliximab-based treatment regimen.

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Steroid-Free Clinical Remission in the SONIC Study

Gary R. Lichtenstein, MD

Biologic therapies have revolutionized the treatment of Crohn's disease (CD) over the past decade, but several questions remain regarding the optimal utilization of these drugs. To answer some of these questions, the Study of Biologic- and Immunomodulator-Naïve Patients in Crohn's Disease (SONIC) trial was conducted to compare the safety and efficacy of the immunomodulator azathioprine alone, the tumor necrosis factor (TNF)–directed antibody infliximab alone, and infliximab in combination with azathioprine.

SONIC Study Design

SONIC was a multicenter, double-blind, randomized, phase III clinical study that enrolled 508 patients from 92 centers between March 2005 and November 2008.[1] The study was comprised of an initial 30-week trial followed by a blinded 20-week extension. Eligible patients were at least 21 years of age and had had moderately to severely active CD for at least 6 weeks, which was defined by a Crohn's Disease Activity Index (CDAI) score between 220 and 450 points.[2] All patients were either corticosteroid-dependent, being considered for their second course of corticosteroid therapy within 12 months, or had not responded when treated for at least 4 weeks with either mesalamine or budesonide. Patients with prior exposure to azathioprine, 6-mercaptopurine, methotrexate, or anti-TNF biologic agents were ineligible for this study.

Randomized patients were stratified according to center, CD duration (<3 years vs ≥3 years), and current systemic corticosteroid dose (<20 mg vs ≥20 mg prednisone, or equivalent, daily). Patients were randomized to 1 of 3 treatment arms: 5 mg/kg intravenous infliximab plus oral placebo (n=169), 2.5 mg/kg oral azathioprine plus placebo infusions (n=170), or a combination of 5 mg/kg intravenous infliximab plus 2.5 mg/kg oral azathioprine (n=169). All oral medications were administered daily; infusions were administered at Weeks 0, 2, and 6, and every 8 weeks thereafter. After 30 weeks of therapy, patients were given the choice to continue their assigned blinded treatment in a 20-week extension trial. Of the 318 patients who completed the initial 30-week trial, 280 chose to enter the extension study.

While enrolled in this study, patients were allowed to continue oral mesalamine therapy; budesonide could be maintained only until Week 14, after which time the dosage was tapered. Among patients who did not receive systemic corticosteroids at baseline, initiation of these drugs was permitted until Week 14; after this point, the corticosteroid dose was tapered.

Baseline characteristics were similar for all study participants, with no significant differences among the 3 treatment arms. The median age of patients was 34 years, approximately half (51.6%) were male, and the vast majority were white (92.8%). The median duration of CD prior to study initiation was 2.3 years, and the mean CDAI score was 287.3±56.7 points. Disease distribution showed a relatively even distribution, with 35.2% of patients having involvement of the ileum only, 23.6% having involvement of the colon only, 41.2% having involvement of both the ileum and colon, and 6.9% having involvement of the proximal gastrointestinal tract. Most patients (72.6%) were not receiving any systemic corticosteroid therapy at baseline, but just over half (54.3%) were receiving 5-aminosalicylic agents.

Primary Efficacy Analysis

The primary efficacy endpoint for the SONIC trial was corticosteroid-free clinical remission at Week 26. This

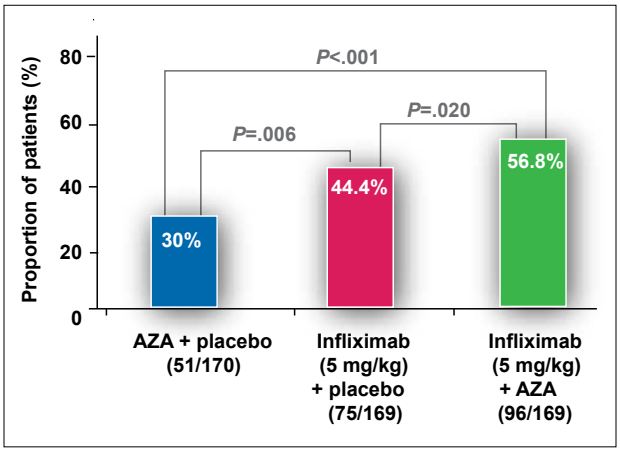

Figure 1. Steroid-free remission at Week 26.

AZA=azathioprine.

endpoint was defined as clinical remission (absolute CDAI score <150 points) in patients who had not received more than 6 mg budesonide daily or systemic corticosteroid therapy for at least 3 weeks. The rate of corticosteroid-free clinical remission at Week 26 was highest in the combination therapy arm (56.8%), followed by the single-agent infliximab (44.4%) and single-agent azathioprine (30.0%) arms (P=.006 for single-agent infliximab vs single-agent azathioprine; P<.001 for combination therapy vs single-agent azathioprine; P=.02 for combination therapy vs single-agent infliximab; Figure 1).

These findings demonstrated that infliximab-based therapy (either monotherapy or infliximab in combination with the immunosuppressant azathioprine) resulted in significantly higher rates of steroid-free remission at Week 26 compared to azathioprine alone for the treatment of patients with moderate-to-severe CD who have failed conventional therapy or who are corticosteroid-dependent.

Impact of SONIC Findings on Clinical Practice

Azathioprine is not approved by the US Food and Drug Administration (FDA) for the treatment of CD and, as such, its contribution to the effectiveness of use in combination with infliximab has not been established. Nonetheless, azathioprine has been a mainstay of CD treatment for several decades. The SONIC study showed that patients receiving azathioprine monotherapy achieved lower rates of steroid-free remission at Week 26 than patients receiving infliximab-based treatments. The SONIC trial therefore has the potential to change clinical practice, as this finding may prompt physicians to rethink the use of single-agent azathioprine treatment versus an infliximab-based treatment regimen in this patient population. The use of azathioprine in combination with infliximab should take into account the potential risks associated with combination therapy and monotherapy.

The fact that more infliximab-treated patients were able to completely discontinue corticosteroid therapy and achieve remission is significant. According to guidelines developed by the American College of Gastroenterology (ACG), goals of CD therapy include inducing and maintaining symptomatic control and minimizing short- and long-term toxicity and complications.[3] Overall, the recommendations in the ACG guidelines align with the primary endpoint of the SONIC trial, as both place an emphasis on achieving corticosteroid-free clinical remission. This endpoint is especially important among patients with CD, as this disease has a characteristically chronic, relapsing course.

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Secondary Efficacy Endpoints in the SONIC Study

Asher Kornbluth, MD

The primary efficacy endpoint of the SONIC study, corticosteroid-free clinical remission at Week 26, is the most stringent criterion used in any of the major CD clinical studies to date. In addition to this endpoint, the design of the SONIC trial also included assessment of several clinically important and relevant secondary endpoints.[1] However, because no adjustments were made for multiple comparisons, the *P* values for comparisons among secondary endpoints should be considered nominal.

Secondary Efficacy Analyses

Both single-agent infliximab and infliximab combined with azathioprine resulted in improvements in clinical response as early as Week 2. Defined as an improvement in CDAI score of at least 70 points, the rate of clinical response at Week 2 was 63.3% for combination therapy, 55.6% for infliximab monotherapy, and 34.1% for azathioprine monotherapy (*P*<.001 for infliximab monotherapy vs azathioprine monotherapy; *P*<.001 for combination therapy vs single-agent azathioprine; *P*=.15 for combination therapy vs infliximab monotherapy). Azathioprine is not approved by the FDA for the treatment of CD and, as such, its contribution to the effectiveness of use in combination with infliximab has not been established. The use of azathioprine in combination with infliximab should take into account the potential risks associated with combination therapy and monotherapy.

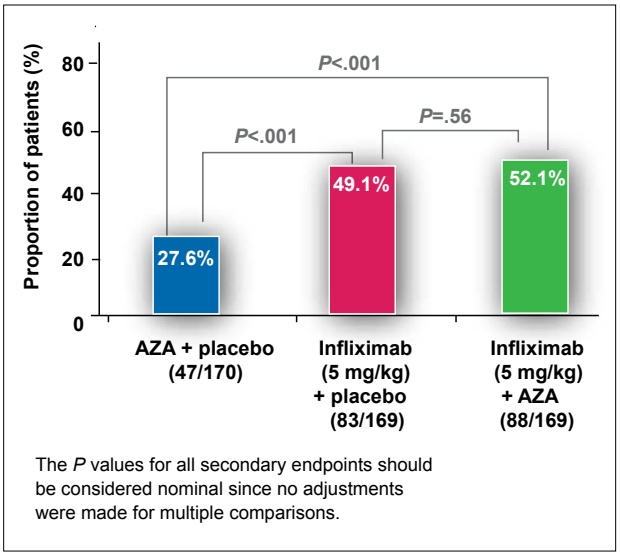

Figure 2. Clinical remission (Crohn's Disease Activity Index score <150 points) at Week 6.

AZA=azathioprine.

Another secondary endpoint in the SONIC study was the rate of clinical remission (defined as an absolute CDAI score <150 points).[2,3] Assessment of clinical remission revealed the same pattern that was seen for the previously discussed endpoint, with improved results in the combination treatment and infliximab monotherapy arms compared to the azathioprine monotherapy arm; higher rates of clinical remission were noted as early as 6 weeks after initiating therapy (52.1%, 49.1%, and 27.6%, respectively; *P*<.001 for single-agent infliximab vs single-agent azathioprine; *P*<.001 for combination therapy vs single-agent azathioprine; *P*=.56 for combination therapy vs single-agent infliximab; Figure 2).

Other secondary endpoints included the rates of corticosteroid-free clinical remission at Weeks 6 and 50 (Figure 3). At 6 weeks, combination therapy and single-agent infliximab treatment showed higher rates of corticosteroid-free clinical remission compared to single-agent azathioprine treatment (32.5%, 29.6%, and 14.1%, respectively; *P*<.001 for single-agent infliximab vs single-agent azathioprine; *P*<.001 for combination therapy vs single-agent azathioprine; *P*=.55 for combination therapy vs single-agent infliximab). This effect proved to be durable, as the Week 50 analysis showed higher rates of corticosteroid-free clinical remission associated with combination therapy and infliximab monotherapy compared to azathioprine monotherapy (46.2%, 34.9%, and 24.1%, respectively; *P*=.03 for single-agent infliximab vs single-agent azathioprine; *P*<.001 for combination therapy vs single-agent azathioprine; *P*=.04 for combination therapy vs single-agent infliximab).

Finally, the SONIC study examined mucosal healing, which was defined as the absence of mucosal ulceration at Week 26 among patients with confirmed mucosal ulceration at baseline. The rate of mucosal healing at Week 26 was higher among patients in the combination treatment arm (43.9%) compared to the infliximab monotherapy (30.1%) and azathioprine monotherapy arms (16.5%; *P*=.02 for single-agent infliximab vs single-agent azathioprine; *P*<.001 for combination therapy vs single-agent azathioprine; *P*=.06 for combination therapy vs single-agent infliximab; Figure 4).

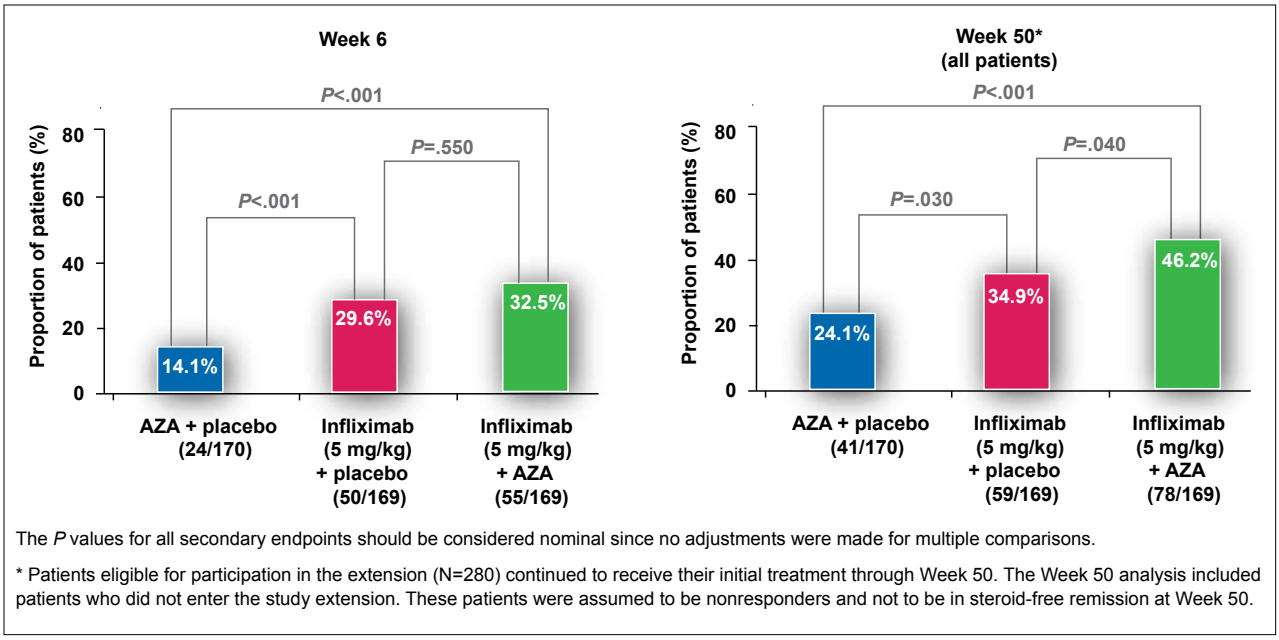

Figure 3. Steroid-free remission at Weeks 6 and 50.

AZA=azathioprine.

Post-hoc Sub-analysis

A trend toward improved rates of corticosteroid-free clinical remission at Week 26 among patients in the combination and single-agent infliximab arms compared with the single-agent azathioprine arm was maintained across several subgroups, including patients with elevated C-reactive protein (CRP) levels (≥0.8 mg/dL) at baseline, patients with mucosal lesions at baseline, and patients with both elevated CRP levels and mucosal lesions at baseline.

Clinical Relevance of Secondary Endpoints

In general, the secondary endpoints in the SONIC trial showed the same trend seen with the primary endpoint. One noteworthy finding, however, is that while the rate of corticosteroid-free clinical remission at Week 6 was higher in the combination therapy and infliximab monotherapy arms than the azathioprine monotherapy arm, little difference was seen between the combination therapy and single-agent infliximab arms at this early time point. One potential explanation for this finding is that azathioprine requires

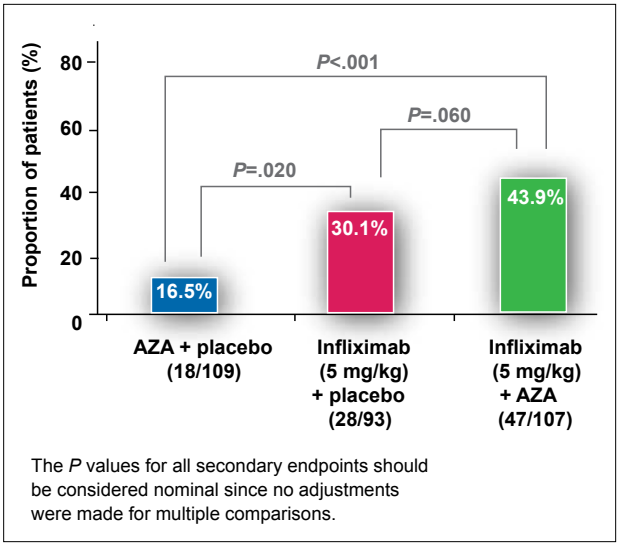

Figure 4. Mucosal healing at Week 26.

AZA=azathioprine.

SELECTED IMPORTANT SAFETY INFORMATION:

Serious and sometimes fatal side effects have been reported with REMICADE® (infliximab), including infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens (e.g., TB, histoplasmosis). Lymphoma (including a rare type of T-cell lymphoma) and other malignancies also have been reported in children and young adult patients. REMICADE® is contraindicated in patients with severe hypersensitivity reactions to REMICADE® and certain patients with congestive heart failure. Other serious side effects include hepatitis B reactivation, hepatotoxicity, hematological events, hypersensitivity, neurological events, and lupus-like syndrome. Please see related and other Important Safety Information on pages 9–15.

a longer duration of time to act in CD, which may have prevented it from providing an additive benefit at 6 weeks.[4] This is supported by the fact that higher rates were observed in the combination therapy arm versus the infliximab monotherapy arm at Week 50 (46.2% vs 34.9%; *P*=.04)

Also, improvements in the response and remission rates among patients receiving infliximab (either in combination with azathioprine or as a single agent) compared with single-agent azathioprine treatment were evident as early as 2 and 6 weeks after initiating therapy. These results are consistent with recommendations from the ACG guidelines, which state that clinical evidence of improvement should be apparent within 2–4 weeks after beginning therapy and that maximal improvement should be achieved within 12–16 weeks.[5]

Finally, mucosal healing is increasingly gaining recognition as an important biologic endpoint and an emerging goal of therapy according to the ACG guidelines.[5] The mucosal healing findings observed in the SONIC study showed a pattern similar to that seen for the achievement of corticosteroid-free clinical remission; that is, patients who received infliximab (either as part of the combination treatment or in the single-agent arm) had a higher rate of mucosal healing than patients who received azathioprine alone.

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Redefining the Infliximab Patient: A Case for Earlier Treatment When Conventional Therapies Fail

Geert D'Haens, MD, PhD

Traditionally, CD has been treated using an approach in which patients are first treated with the least potent but safest therapies and are gradually introduced to more potent but higher-risk agents as the disease progresses.[1] Recently, however, some clinicians have begun to consider earlier introduction of potent therapies such as anti-TNF biologic agents after the failure of conventional therapies.

Demonstrating Efficacy with Earlier Treatment

Three types of patients with moderately to severely active CD were included in the SONIC trial: those who were corticosteroid-dependent, those who were being considered for their second course of corticosteroids within a period of 12 months or less, and those who had not shown a response to at least 4 weeks of either 5-aminosalicylate or budesonide therapy. The baseline characteristics of the patients enrolled in the SONIC trial revealed that the median duration of CD prior to study randomization was 2.3 years (2.2, 2.2, and 2.4 years for the combination treatment, infliximab-only, and azathioprine-only groups, respectively).[2] These patients were thus much earlier in the course of their disease than patients enrolled in other major clinical trials involving biologic therapy. For example, in the ACCENT I study, which assessed the benefit of infliximab as maintenance therapy for CD, the median duration of CD was 7.9 years (range: 3.9–14.7 years).[3]

The incidence of adverse events was generally similar across all 3 treatment arms (Table 1). The primary difference in adverse events was the incidence of infusion reactions, which was higher in the infliximab-only arm (16.6%) than the combination therapy (5.0%) or azathioprine-only arms (5.6%; *P*=.002 for single-agent infliximab vs single-agent azathioprine; *P*=1.00 for combination therapy vs single-agent azathioprine; *P*<.001 for combination therapy vs single-agent infliximab). The incidence of severe adverse events was actually lower in the combination therapy arm (15.1%) than either the infliximab monotherapy (23.9%) or azathioprine monotherapy arms (26.7%); the rate of serious infections was similar across the 3 treatment groups (3.9%, 4.9%, and 5.6%, respectively). Adverse events that were reported in more than 10% of patients in any of the treatment arms included nausea, abdominal pain, CD worsening, vomiting, diarrhea, fatigue, pyrexia, arthralgia, headache, and nasopharyngitis.

Recommendation for Earlier Treatment in Clinical Practice

Two important points were demonstrated by the SONIC trial. First, results from this study suggest that if infliximab

Table 1. Safety Data Through Week 54: Incidence of Adverse Events Was Generally Similar Among the 3 Treatment Groups*

	AZA + placebo n=161	Infliximab + placebo n=163	Infliximab + AZA n=179
Patients with any AE, n (%)	144 (89.4%)	145 (89%)	161 (89.9%)
Serious AEs, n (%)	43 (26.7%)	39 (23.9%)	27 (15.1%)
AEs leading to study drug discontinuation, n (%)	42 (26.1%)	29 (17.8%)	37 (20.7%)
Serious infections, n (%)	9 (5.6%)	8 (4.9%)	7 (3.9%)
Number of patients with infusion reactions (%)†	9 (5.6%)	27 (16.6%)	9 (5%)
Total number of infusions/ number of infusions with infusion reactions (%)	862/10 (1.2%)	990/45 (4.5%)	1,097/11 (1%)

*All treated subjects.

†For patients with mild-to-moderate reactions who do not tolerate the infusion following appropriate interventions or have severe reactions, infliximab should be discontinued.

AE=adverse event; AZA=azathioprine.

is going to be initiated in a patient with CD who has not been previously exposed to an immunomodulatory agent, then either infliximab monotherapy or infliximab in combination with azathioprine should be considered, as either regimen may be more effective than azathioprine monotherapy. Azathioprine is not approved by the FDA for the treatment of CD and, as such, its contribution to the effectiveness of use in combination with infliximab has not been established. The use of azathioprine in combination with infliximab should take into account the potential risks associated with combination therapy and monotherapy. The second finding is that there may be no need to continue corticosteroid therapy for a long period while waiting to initiate infliximab; instead, if a patient's disease warrants the use of infliximab, then physicians may want to initiate this agent promptly, so that the corticosteroid can be tapered as soon as possible.

The results of the SONIC trial have now been available to clinicians for almost 1 year; in that time, it has become apparent that these data have the potential to change clinical practice. In the current treatment paradigm, physicians often wait until patients fail several first-line therapies before initiating treatment with a biologic agent, taking into consideration the risks and benefits of such treatment. Based on mounting clinical data, including the SONIC study, it is becoming increasingly apparent that many patients may benefit from earlier introduction of infliximab after the failure of conventional therapies. This realization is reflected in the current ACG clinical practice guidelines, which state that "infliximab monotherapy and infliximab combined with azathioprine are more effective than azathioprine in the treatment of patients with moderate to severe CD who have failed to respond to first-line therapy with mesalamine and/or corticosteroids and are naïve to immunosuppressive and biologic agents."[4]

Although approved for the treatment of patients with moderately to severely active CD who had an inadequate response to conventional therapies, many questions remain regarding the use of infliximab in these patients. To address these issues, clinical studies such as the SONIC trial are providing an increasing amount of data that can help to better define the role of infliximab in the CD treatment paradigm.

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IMPORTANT SAFETY INFORMATION FOR REMICADE® (infliximab)

SERIOUS INFECTIONS

Patients treated with REMICADE® (infliximab) 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 REMICADE® if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before and during treatment with REMICADE®.[1,2] Treatment for latent infection should be initiated prior to treatment with REMICADE®.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, and pneumocystosis. Patients may present with disseminated, rather than localized, disease. Empiric antifungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with REMICADE® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with REMICADE®, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

In clinical trials, other serious infections observed in patients treated with REMICADE® included pneumonia, cellulitis, abscess, and skin ulceration.

MALIGNANCIES

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including REMICADE®. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months after the first dose of therapy. Most of the patients were receiving concomitant immunosuppressants.

Postmarketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including REMICADE®. These cases have had a very aggressive disease course and have been fatal. All reported REMICADE® cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with REMICADE® at or prior to diagnosis. Carefully assess the risks and benefits of treatment with REMICADE®, especially in these patient types.

In clinical trials of all TNF inhibitors, more cases of lymphoma were observed compared with controls and the expected rate in the general population. However, patients with Crohn's disease, rheumatoid arthritis, or plaque psoriasis may be at higher risk for developing lymphoma. In clinical trials of some TNF inhibitors, including REMICADE®, more cases of other malignancies were observed compared with controls. The rate of these malignancies among patients treated with REMICADE® was similar to that expected in the general population whereas the rate in control patients was lower than expected. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use. As the potential role of TNF inhibitors in the development of malignancies is not known, caution should be exercised when considering treatment of patients with a current or a past history of malignancy or other risk factors such as chronic obstructive pulmonary disease (COPD).

CONTRAINDICATIONS

REMICADE® is contraindicated in patients with moderate to severe (NYHA Class III/IV) congestive heart failure (CHF) at doses greater than 5 mg/kg. Higher mortality rates at the 10 mg/kg dose and higher rates of cardiovascular events at the 5 mg/kg dose have been observed in these patients. REMICADE® should be used with caution and only after consideration of other treatment options. Patients should be monitored closely. Discontinue REMICADE® if new or worsening CHF symptoms appear. REMICADE® should not be (re)administered to patients who have experienced a severe hypersensitivity reaction or to patients with hypersensitivity to murine proteins or other components of the product.

HEPATITIS B REACTIVATION

TNF inhibitors, including REMICADE®, have been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases were fatal. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating REMICADE®. Exercise caution when prescribing

(Continued on next page)

IMPORTANT SAFETY INFORMATION FOR REMICADE® *(CONTINUED)*

REMICADE® for patients identified as carriers of HBV and monitor closely for active HBV infection during and following termination of therapy with REMICADE®. Discontinue REMICADE® in patients who develop HBV reactivation and initiate antiviral therapy with appropriate supportive treatment. Exercise caution when considering resumption of REMICADE® and monitor patients closely.

HEPATOTOXICITY

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis have been reported rarely in patients receiving REMICADE® postmarketing. Some cases were fatal or required liver transplant. Aminotransferase elevations were not noted prior to discovery of liver injury in many cases. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develop, REMICADE® should be discontinued, and a thorough investigation of the abnormality should be undertaken.

HEMATOLOGIC EVENTS

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia (some fatal) have been reported. The causal relationship to REMICADE® therapy remains unclear. Exercise caution in patients who have ongoing or a history of significant hematologic abnormalities. Advise patients to seek immediate medical attention if they develop signs and symptoms of blood dyscrasias or infection. Consider discontinuation of REMICADE® in patients who develop significant hematologic abnormalities.

HYPERSENSITIVITY

REMICADE® has been associated with hypersensitivity reactions that differ in their time of onset. Acute urticaria, dyspnea, and hypotension have occurred in association with infusions of REMICADE®. Serious infusion reactions including anaphylaxis were infrequent. Medications for the treatment of hypersensitivity reactions should be available.

NEUROLOGIC EVENTS

TNF inhibitors, including REMICADE®, have been associated in rare cases with CNS manifestation of systemic vasculitis, seizure, and new onset or exacerbation of CNS demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Exercise caution when considering REMICADE® in patients with these disorders and consider discontinuation if these disorders develop.

AUTOIMMUNITY

Treatment with REMICADE® may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

ADVERSE REACTIONS

In clinical trials, the most common REMICADE® adverse reactions occurring in >10% of patients included infections (e.g., upper respiratory, sinusitis, and pharyngitis), infusion-related reactions, headache, and abdominal pain.

USE WITH OTHER DRUGS

The use of REMICADE® in combination with anakinra, abatacept or tocilizumab is not recommended. Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection. Live vaccines should not be given with REMICADE®. Bring pediatric Crohn's patients up to date with all vaccinations prior to initiating REMICADE®.

Please see Brief Summary of full Prescribing Information accompanying this advertisement.

References:

1. American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med.* 2000;161:S221–S247.
2. See latest Centers for Disease Control guidelines and recommendations for tuberculosis testing in immunocompromised patients.

REMICADE (infliximab)
Lyophilized Concentrate for Intravenous (IV) Injection
Brief Summary of Full Prescribing Information

WARNINGS
SERIOUS INFECTIONS
Patients treated with REMICADE® are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions and Adverse Reactions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

REMICADE should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before REMICADE use and during therapy.[1,2] Treatment for latent infection should be initiated prior to REMICADE use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with REMICADE should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with REMICADE, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCY
Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including REMICADE *[see Warnings and Precautions]*.

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

CONTRAINDICATIONS: REMICADE at doses >5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating REMICADE in patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), REMICADE treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure *[see Warnings and Precautions and Adverse Reactions]*. REMICADE should not be re-administered to patients who have experienced a severe hypersensitivity reaction to REMICADE. Additionally, REMICADE should not be administered to patients with known hypersensitivity to inactive components of the product or to any murine proteins.
WARNINGS AND PRECAUTIONS (see Boxed WARNINGS): Serious Infections: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving TNF-blocking agents. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly reported. Patients have frequently presented with disseminated rather than localized disease, and are often taking concomitant immunosuppressants such as methotrexate or corticosteroids with REMICADE. Treatment with REMICADE should not be initiated in patients with an active infection, including clinically important localized infections. The risks and benefits of treatment should be considered prior to initiating therapy in patients: • with chronic or recurrent infection; • who have been exposed to tuberculosis; • who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or • with underlying conditions that may predispose them to infection. Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving REMICADE, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating REMICADE and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating REMICADE, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG). Anti-tuberculosis therapy should also be considered prior to initiation of REMICADE in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of

tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Tuberculosis should be strongly considered in patients who develop a new infection during REMICADE treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with REMICADE, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with REMICADE. REMICADE should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with REMICADE should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated. For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy. **Malignancies:** Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), including REMICADE. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal. All reported REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. All of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with REMICADE at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to REMICADE or REMICADE in combination with these other immunosuppressants. When treating patients with inflammatory bowel disease, particularly in adolescents and young adults, consideration of whether to use REMICADE alone or in combination with other immunosuppressants should take into account a possibility that there is a higher risk of HSTCL with combination therapy versus an observed increased risk of immunogenicity and hypersensitivity reactions with REMICADE monotherapy from the clinical trial data *[see Warnings and Precautions and Adverse Reactions, Immunogenicity]*. In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE, more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been observed in patients receiving those TNF-blockers compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 14 patients were diagnosed with malignancies (excluding lymphoma and NMSC) among 4019 REMICADE-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among REMICADE-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for REMICADE-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among REMICADE-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected. In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of REMICADE clinical trials, 5 patients developed lymphomas among 5707 patients treated with REMICADE (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population. Patients with Crohn's disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia. In a clinical trial exploring the use of REMICADE in patients with moderate to severe chronic obstructive pulmonary disease

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(COPD), more malignancies, the majority of lung or head and neck origin, were reported in REMICADE-treated patients compared with control patients. All patients had a history of heavy smoking *[see Adverse Reactions]*. Prescribers should exercise caution when considering the use of REMICADE in patients with moderate to severe COPD. Psoriasis patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for REMICADE, NMSCs were more common in patients with previous phototherapy *[see Adverse Reactions]*. The potential role of TNF-blocking therapy in the development of malignancies is not known *[see Adverse Reactions]*. Rates in clinical trials for REMICADE cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering REMICADE treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving REMICADE. **Hepatitis B Virus Reactivation:** Use of TNF blockers, including REMICADE, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers, including REMICADE, for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF blocker therapy in this situation and monitor patients closely. **Hepatotoxicity:** Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis, have been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between 2 weeks to more than 1 year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develop, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE without progression to severe hepatic injury *[see Adverse Reactions]*. **Patients with Heart Failure:** REMICADE has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of REMICADE in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE should be discontinued if new or worsening symptoms of heart failure appear *[see Contraindications and Adverse Reactions]*. **Hematologic Events:** Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE. The causal relationship to REMICADE therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with REMICADE who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on REMICADE. Discontinuation of REMICADE therapy should be considered in patients who develop significant hematologic abnormalities. **Hypersensitivity:** REMICADE has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE infusion. However, in some cases, serum sickness-like reactions have been observed in patients after initial REMICADE therapy (i.e., as early as after the second dose), and when REMICADE therapy was reinstituted following an extended period without REMICADE treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with a marked increase in antibodies to infliximab, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy. REMICADE should be discontinued for severe hypersensitivity reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction *[see Adverse Reactions]*. In rheumatoid arthritis, Crohn's disease and psoriasis clinical trials, re-administration of REMICADE after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment *[see Adverse Reactions]*. In general, the benefit-risk of re-administration of REMICADE after a period of no-treatment, especially as a re-induction regimen given at weeks 0, 2 and 6, should be carefully considered. In the case where REMICADE maintenance therapy for psoriasis is interrupted, REMICADE should be reinitiated as a single dose followed by maintenance therapy. **Neurologic Events:** REMICADE and other agents that inhibit TNF have been associated in rare cases with CNS manifestation of systemic vasculitis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of REMICADE in patients with these neurologic disorders and should consider discontinuation of REMICADE if these disorders develop. **Use with Anakinra:** Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNFα-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNFα-blocking agents. Therefore, the combination of REMICADE and anakinra is not recommended. **Use with Abatacept:** In clinical studies, concurrent administration of TNF-blocking agents and abatacept have been associated with an increased risk of infections including serious infections compared with TNF-blocking agents alone, without increased clinical benefit. Therefore, the combination of REMICADE and abatacept is not recommended *[see Drug Interactions]*. **Switching between Biological Disease-Modifying Antirheumatic Drugs (DMARDs):** Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection. **Autoimmunity:** Treatment with REMICADE may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REMICADE, treatment should be discontinued *[see Adverse Reactions]*. **Vaccinations:** No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently. It is recommended that all pediatric Crohn's disease patients be brought up to date with all vaccinations prior to initiating REMICADE therapy. The interval between vaccination and initiation of REMICADE therapy should be in accordance with current vaccination guidelines. **ADVERSE REACTIONS: Clinical Studies Experience:** The data described herein reflect exposure to REMICADE in 4779 adult patients (1304 patients with rheumatoid arthritis, 1106 patients with Crohn's disease, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 484 with ulcerative colitis, 1373 with plaque psoriasis, and 17 patients with other conditions), including 2625 patients exposed beyond 30 weeks and 374 exposed beyond 1 year. *[For information on adverse reactions in pediatric patients see Adverse Reactions.]* One of the most-common reasons for discontinuation of treatment was infusion-related reactions (e.g., dyspnea, flushing, headache and rash). Adverse events have been reported in a higher proportion of rheumatoid arthritis patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no differences were observed in the frequency of adverse events between the 5 mg/kg dose and 10 mg/kg dose in patients with Crohn's disease. ***Infusion-related Reactions:*** An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 to 2 hours after an infusion. Approximately 20% of REMICADE-treated patients in all clinical studies experienced an infusion reaction compared to approximately 10% of placebo-treated patients. Among all REMICADE infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued REMICADE because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial infusion were not associated with a higher incidence of reactions. The infusion reaction rates remained stable in psoriasis through 1 year in psoriasis Study I. In psoriasis Study II, the rates were variable over time and somewhat higher following the final infusion than after the initial infusion. Across the 3 psoriasis studies, the percent of total infusions resulting in infusion reactions (i.e., an adverse event occurring within 1 to 2 hours) was 7% in the 3 mg/kg group, 4% in the 5 mg/kg group, and 1% in the placebo group. Patients who became positive for antibodies to infliximab were more likely (approximately two- to three-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of both antibodies to infliximab and infusion reactions *[see Adverse Reactions and Drug Interactions]*. ***Infusion reactions following re-administration:*** In a clinical trial of patients with moderate to severe psoriasis designed to assess the efficacy of long-term maintenance therapy versus re-treatment with an induction regimen of REMICADE following disease flare, 4% (8/219) of patients in the re-treatment therapy arm experienced serious infusion reactions versus < 1% (1/222) in the maintenance therapy arm. Patients enrolled in this trial did not receive any concomitant immunosuppressant therapy. In this study, the majority of serious infusion reactions occurred during the second infusion at Week 2. Symptoms included, but were not limited to, dyspnea, urticaria, facial edema, and hypotension. In all cases, REMICADE treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed Reactions/Reactions Following Re-administration: *Plaque Psoriasis:* In psoriasis studies, approximately 1% of REMICADE-treated patients experienced a possible delayed hypersensitivity reaction, generally reported as serum sickness or a combination of arthralgia and/or myalgia with fever and/or rash. These reactions generally occurred within 2 weeks after repeat infusion. *Crohn's disease:* In a study where 37 of 41 patients with Crohn's disease were retreated with infliximab following a 2- to 4-year period without infliximab treatment, 10 patients experienced adverse events manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache. Patients experiencing these adverse events had not experienced infusion-related adverse events associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients who received lyophilized formulation. The clinical data are not adequate to determine if occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms improved substantially or resolved with treatment in all cases. There are insufficient data on the incidence of these events after drug-free intervals of 1 to 2 years. These events have been observed only infrequently in clinical studies and post-marketing surveillance with retreatment intervals up to 1 year. ***Infections:*** In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of these cases of tuberculosis occurred within the first 2 months after initiation of therapy with REMICADE and may reflect recrudescence of latent disease *[see Warnings and Precautions]*. In the 1-year placebo-controlled studies RA I and RA II, 5.3% of patients receiving REMICADE every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients receiving MTX. Of 924 patients receiving REMICADE, 1.7% developed pneumonia and 0.4% developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg or 10 mg/kg REMICADE infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX, serious infections were more frequent in the 10 mg/kg REMICADE group (5.3%) than the 3 mg/kg or placebo groups (1.7% in both). During the 54-week Crohn's II Study, 15% of patients with fistulizing Crohn's disease developed a new fistula-related abscess. In REMICADE clinical studies in patients with ulcerative colitis, infections treated with antimicrobials were reported in 27% of REMICADE-treated patients (average of 41 weeks of follow-up) and in 18% of placebo-treated patients (average 32 weeks of follow-up). The types of infections, including serious infections, reported in patients with ulcerative colitis were similar to those reported in other clinical studies. In post-marketing experience in the various indications, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving REMICADE alone or in combination with immunosuppressive agents. The onset of serious infections may be preceded by constitutional symptoms such as fever, chills, weight loss, and fatigue. The majority of serious infections, however, may also be preceded by signs or symptoms localized to the site of the infection. ***Autoantibodies/Lupus-like Syndrome:*** Approximately half of REMICADE-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately one-fifth of REMICADE-treated patients compared with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon. ***Malignancies:*** In controlled trials, more REMICADE-treated patients developed malignancies than placebo-treated patients *[see Warnings and Precautions]*. In a randomized controlled clinical trial exploring the use of REMICADE in patients with moderate to severe COPD who were either current smokers or ex-smokers, 157 patients were treated with REMICADE at doses similar to those used in rheumatoid arthritis and Crohn's disease. Of these REMICADE-treated patients, 9 developed a malignancy, including 1 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 3.51 - 14.56). There was 1 reported malignancy among 77 control patients for a rate of 1.63 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 0.04 - 9.10). The majority of the malignancies developed in the lung or head and neck. Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been reported in patients receiving REMICADE during post-approval use. ***Patients with Heart Failure:*** In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction ≤35%), 150 patients were randomized to receive treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the placebo groups. There were trends toward increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and

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5 mg/kg REMICADE treatment groups, versus placebo. REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II) *[see Contraindications and Warnings and Precautions]*. ***Immunogenicity:*** Treatment with REMICADE can be associated with the development of antibodies to infliximab. The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through 1 to 2 years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving REMICADE after drug-free intervals >16 weeks. In a study of psoriatic arthritis in which 191 patients received 5 mg/kg with or without MTX, antibodies to infliximab occurred in 15% of patients. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction *[see Adverse Reactions]* than were patients who were antibody negative. Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX. In the psoriasis Study II, which included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 36% of patients treated with 5 mg/kg every 8 weeks for 1 year, and in 51% of patients treated with 3 mg/kg every 8 weeks for 1 year. In the psoriasis Study III, which also included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 20% of patients treated with 5 mg/kg induction (weeks 0, 2 and 6), and in 27% of patients treated with 3 mg/kg induction. Despite the increase in antibody formation, the infusion reaction rates in Studies I and II in patients treated with 5 mg/kg induction followed by every 8 week maintenance for 1 year and in Study III in patients treated with 5 mg/kg induction (14.1%-23.0%) and serious infusion reaction rates (<1%) were similar to those observed in other study populations. The clinical significance of apparent increased immunogenicity on efficacy and infusion reactions in psoriasis patients as compared to patients with other diseases treated with REMICADE over the long term is not known. The data reflect the percentage of patients whose test results were positive for antibodies to infliximab in an ELISA assay, and they are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to infliximab with the incidence of antibodies to other products may be misleading. ***Hepatotoxicity:*** Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported rarely in patients receiving REMICADE *[see Warnings and Precautions]*. Reactivation of hepatitis B virus has occurred in patients receiving TNF-blocking agents, including REMICADE, who are chronic carriers of this virus *[see Warnings and Precautions]*. In clinical trials in rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving REMICADE than in controls (Table 1), both when REMICADE was given as monotherapy and when it was used in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of REMICADE, or modification of concomitant medications.

Table 1 Proportion of patients with elevated ALT in clinical trials

	Proportion of patients with elevated ALT					
	>1 to <3 x ULN		≥3 x ULN		≥5 x ULN	
	Placebo	REMICADE	Placebo	REMICADE	Placebo	REMICADE
Rheumatoid arthritis[a]	24%	34%	3%	4%	<1%	<1%
Crohn's disease[b]	34%	39%	4%	5%	0%	2%
Ulcerative colitis[c]	12%	17%	1%	2%	<1%	<1%
Ankylosing spondylitis[d]	15%	51%	0%	10%	0%	4%
Psoriatic arthritis[e]	16%	50%	0%	7%	0%	2%
Plaque psoriasis[f]	24%	49%	<1%	8%	0%	3%

[a]Placebo patients received methotrexate while REMICADE patients received both REMICADE and methotrexate. Median follow-up was 58 weeks. [b]Placebo patients in the 2 Phase 3 trials in Crohn's disease received an initial dose of 5 mg/kg REMICADE at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to REMICADE are included in the REMICADE group in ALT analysis. Median follow-up was 54 weeks. [c]Median follow-up was 30 weeks. Specifically, the median duration of follow-up was 30 weeks for placebo and 31 weeks for REMICADE. [d]Median follow-up was 24 weeks for placebo group and 102 weeks for REMICADE group. [e]Median follow-up was 39 weeks for REMICADE group and 18 weeks for placebo group. [f]ALT values are obtained in 2 Phase 3 psoriasis studies with median follow-up of 50 weeks for REMICADE and 16 weeks for placebo.

Adverse Reactions in Pediatric Crohn's Disease: There were some differences in the adverse reactions observed in the pediatric patients receiving REMICADE compared to those observed in adults with Crohn's disease. These differences are discussed in the following paragraphs. The following adverse events were reported more commonly in 103 randomized pediatric Crohn's disease patients administered 5 mg/kg REMICADE through 54 weeks than in 385 adult Crohn's disease patients receiving a similar treatment regimen: anemia (11%), blood in stool (10%), leukopenia (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%). Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn's and in 50% of adult patients in Study Crohn's I. In Study Peds Crohn's, infections were reported more frequently for patients who received every 8-week as opposed to every 12-week infusions (74% and 38%, respectively), while serious infections were reported for 3 patients in the every 8-week and 4 patients in the every 12-week

maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported for 3 patients, (2 in the every 8-week and 1 in the every 12-week maintenance treatment groups). Herpes zoster was reported for 2 patients in the every 8-week maintenance treatment group. In Study Peds Crohn's, 18% of randomized patients experienced 1 or more infusion reactions, with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn's, there were no serious infusion reactions, and 2 patients had non-serious anaphylactoid reactions. In Study Peds Crohn's, in which all patients received stable doses of 6-MP, AZA, or MTX, 3% (3/105) of patients developed antibodies to REMICADE. Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric patients in Crohn's disease clinical trials; 4% had ALT elevations ≥3 x ULN, and 1% had elevations ≥5 x ULN. (Median follow-up was 53 weeks.) ***Adverse Reactions in Psoriasis Studies:*** During the placebo-controlled portion across the 3 clinical trials up to week 16, the proportion of patients who experienced at least 1 SAE (defined as resulting in death, life threatening, requires hospitalization, or persistent or significant disability/incapacity) was 1.7% in the 3 mg/kg REMICADE group, 3.2% in the placebo group, and 3.9% in the 5 mg/kg REMICADE group. Among patients in the 2 Phase 3 studies, 12.4% of patients receiving REMICADE 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 SAE in Study I. In Study II, 4.1% and 4.7% of patients receiving REMICADE 3 mg/kg and 5 mg/kg every 8 weeks, respectively, through 1 year of maintenance treatment experienced at least 1 SAE. One death due to bacterial sepsis occurred 25 days after the second infusion of 5 mg/kg REMICADE. Serious infections included sepsis, and abscesses. In Study I, 2.7% of patients receiving REMICADE 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 serious infection. In Study II, 1.0% and 1.3% of patients receiving REMICADE 3 mg/kg and 5 mg/kg, respectively, through 1 year of treatment experienced at least 1 serious infection. The most common serious infection (requiring hospitalization) was abscess (skin, throat, and peri-rectal) reported by 5 (0.7%) patients in the 5 mg/kg REMICADE group. Two active cases of tuberculosis were reported: 6 weeks and 34 weeks after starting REMICADE. In the placebo-controlled portion of the psoriasis studies, 7 of 1123 patients who received REMICADE at any dose were diagnosed with at least one NMSC compared to 0 of 334 patients who received placebo. In the psoriasis studies, 1% (15/1373) of patients experienced serum sickness or a combination of arthralgia and/or myalgia with fever, and/or rash, usually early in the treatment course. Of these patients, 6 required hospitalization due to fever, severe myalgia, arthralgia, swollen joints, and immobility. ***Other Adverse Reactions:*** Safety data are available from 4779 REMICADE-treated adult patients, including 1304 with rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 1373 with plaque psoriasis and 17 with other conditions. *[For information on other adverse reactions in pediatric patients, see Adverse Reactions].* Adverse events reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are in Table 2. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and Crohn's disease patients except for abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons.

Table 2 Adverse reactions occurring in 5% or more of patients receiving 4 or more infusions for rheumatoid arthritis

	Placebo	REMICADE
	(n=350)	(n=1129)
Average weeks of follow-up	59	66
Gastrointestinal		
Nausea	20%	21%
Abdominal pain	8%	12%
Diarrhea	12%	12%
Dyspepsia	7%	10%
Respiratory		
Upper respiratory tract infection	25%	32%
Sinusitis	8%	14%
Pharyngitis	8%	12%
Coughing	8%	12%
Bronchitis	9%	10%
Skin and appendages disorders		
Rash	5%	10%
Pruritus	2%	7%
Body as a whole-general disorders		
Fatigue	7%	9%
Pain	7%	8%
Resistance mechanism disorders		
Fever	4%	7%
Moniliasis	3%	5%
Central and peripheral nervous system disorders		
Headache	14%	18%
Musculoskeletal system disorders		
Arthralgia	7%	8%
Urinary system disorders		
Urinary tract infection	6%	8%
Cardiovascular disorders, general		
Hypertension	5%	7%

REMICADE® (infliximab)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice. The most common serious adverse reactions observed in clinical trials were infections *[see Adverse Reactions]*. Other serious, medically relevant adverse reactions ≥0.2% or clinically significant adverse reactions by body system were as follows: *Body as a whole:* allergic reaction, edema; *Blood:* pancytopenia; *Cardiovascular:* hypotension; *Gastrointestinal:* constipation, intestinal obstruction; *Central and Peripheral Nervous:* dizziness; *Heart Rate and Rhythm:* bradycardia; *Liver and Biliary:* hepatitis; *Metabolic and Nutritional:* dehydration; *Platelet, Bleeding and Clotting:* thrombocytopenia; *Neoplasms:* lymphoma; *Red Blood Cell:* anemia, hemolytic anemia; *Resistance Mechanism:* cellulitis, sepsis, serum sickness; *Respiratory:* lower respiratory tract infection (including pneumonia), pleurisy, pulmonary edema; *Skin and Appendages:* increased sweating; *Vascular (Extracardiac):* thrombophlebitis; *White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy. **Post-marketing Experience:** Adverse reactions have been reported during post approval use of REMICADE in adult and pediatric patients. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to REMICADE exposure. The following adverse reactions, some with fatal outcome, have been reported during post-approval use of REMICADE: neutropenia *[see Warnings and Precautions]*, interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis and very rare rapidly progressive disease), idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), new onset and worsening psoriasis (all subtypes including pustular, primarily palmoplantar), transverse myelitis, and neuropathies (additional neurologic events have also been observed) *[see Warnings and Precautions]* and acute liver failure, jaundice, hepatitis, and cholestasis *[see Warnings and Precautions]*. ***Infusion-related Reactions:*** In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with REMICADE administration. Cases of myocardial ischemia/infarction and transient visual loss have also been rarely reported in association with REMICADE during or within 2 hours of infusion. ***Adverse Reactions in Pediatric Patients:*** The following serious adverse reactions have been reported in the post-marketing experience in children: infections (some fatal) including opportunistic infections and tuberculosis, infusion reactions, and hypersensitivity reactions. Serious adverse reactions in the post-marketing experience with REMICADE in the pediatric population have also included malignancies, including hepatosplenic T-cell lymphomas *[see Boxed WARNINGS and Warnings and Precautions]*, transient hepatic enzyme abnormalities, lupus-like syndromes, and the development of autoantibodies. **DRUG INTERACTIONS: Use with Anakinra or Abatacept:** An increased risk of serious infections was seen in clinical studies of other TNFα-blocking agents used in combination with anakinra or abatacept, with no added clinical benefit. Because of the nature of the adverse events seen with these combinations with TNF-blocker therapy, similar toxicities may also result from the combination of anakinra or abatacept with other TNFα-blocking agents. Therefore, the combination of REMICADE and anakinra or abatacept is not recommended *[see Warnings and Precautions]*. **Use with Tocilizumab:** The use of tocilizumab in combination with biological DMARDs such as TNF antagonists, including REMICADE, should be avoided because of the possibility of increased immunosuppression and increased risk of infection. **Methotrexate (MTX) and Other Concomitant Medications:** Specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents (NSAIDs), folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications included MTX in approximately half of the patients as well as NSAIDs, folic acid and corticosteroids. Concomitant MTX use may decrease the incidence of anti-infliximab antibody production and increase infliximab concentrations. **Immunosuppressants:** Patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants *[see Adverse Reactions]*. Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates. **USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category B.** It is not known whether REMICADE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. REMICADE should be given to a pregnant woman only if clearly needed. Because infliximab does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with REMICADE. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. **Nursing Mothers:** It is not known whether REMICADE is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from

REMICADE, women should not breast-feed their infants while taking REMICADE. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy *[see Boxed WARNINGS, Warnings and Precautions, Indications and Usage (1.1) in full Prescribing Information, Dosage and Administration (2.1) in full Prescribing Information, Clinical Studies (14.1) in full Prescribing Information, and Adverse Reactions]*. Remicade has been studied only in combination with conventional immunosuppressive therapy in children with Crohn's disease. REMICADE has not been studied in children with Crohn's disease <6 years of age. Use of REMICADE in the absence of other immunosuppressants may increase the likelihood of infliximab-specific antibody formation and increase the risk of developing hypersensitivity reactions *[see Warnings and Precautions and Adverse Reactions, Immunogenicity]*. The longer term (greater than 1 year) safety and effectiveness of REMICADE in pediatric Crohn's disease patients have not been established in clinical trials. Safety and effectiveness of REMICADE in pediatric patients with ulcerative colitis and plaque psoriasis have not been established. The safety and efficacy of REMICADE in patients with juvenile rheumatoid arthritis (JRA) were evaluated in a multicenter, randomized, placebo-controlled, double-blind study for 14 weeks, followed by a double-blind, all-active treatment extension, for a maximum of 44 weeks. Patients with active JRA between the ages of 4 and 17 years who had been treated with MTX for at least 3 months were enrolled. Concurrent use of folic acid, oral corticosteroids (≤0.2 mg/kg/day of prednisone or equivalent), NSAIDs, and/or disease modifying antirheumatic drugs (DMARDs) was permitted. Doses of 3 mg/kg REMICADE or placebo were administered intravenously at Weeks 0, 2 and 6. Patients randomized to placebo crossed-over to receive 6 mg/kg REMICADE at Weeks 14, 16, and 20, and then every 8 weeks through Week 44. Patients who completed the study continued to receive open-label treatment with REMICADE for up to 2 years in a companion extension study. The study failed to establish the efficacy of REMICADE in the treatment of JRA. Key observations in the study included a high placebo response rate and a higher rate of immunogenicity than what has been observed in adults. Additionally, a higher rate of clearance of infliximab was observed than had been observed in adults *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. A total of 60 patients with JRA were treated with doses of 3 mg/kg and 57 patients were treated with doses of 6 mg/kg. The proportion of patients with infusion reactions who received 3 mg/kg REMICADE was 35% (21/60) over 52 weeks compared with 18% (10/57) in patients who received 6 mg/kg over 38 weeks. The most common infusion reactions reported were vomiting, fever, headache, and hypotension. In the 3 mg/kg REMICADE group, 4 patients had a serious infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among the serious infusion reactions). In the 6 mg/kg REMICADE group, 2 patients had a serious infusion reaction, 1 of whom had a possible anaphylactic reaction. Two of the 6 patients who experienced serious infusion reactions received REMICADE by rapid infusion (duration of less than 2 hours). Antibodies to infliximab developed in 38% (20/53) of patients who received 3 mg/kg REMICADE compared with 12% (6/49) of patients who received 6 mg/kg. A total of 68% (41/60) of patients who received 3 mg/kg REMICADE in combination with MTX experienced an infection over 52 weeks compared with 65% (37/57) of patients who received 6 mg/kg REMICADE in combination with MTX over 38 weeks. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was pneumonia. Other notable infections included primary varicella infection in 1 patient and herpes zoster in 1 patient. **Geriatric Use:** In rheumatoid arthritis and plaque psoriasis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque psoriasis, aged 65 or older who received REMICADE, compared to younger patients—although the incidence of serious adverse events in patients aged 65 or older was higher in both REMICADE and control groups compared to younger patients. In Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly *[see Adverse Reactions]*. **OVERDOSAGE:** Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately. **REFERENCES:** 1. American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;161:S221-S247. 2. See latest Centers for Disease Control guidelines and recommendations for tuberculosis testing in immunocompromised patients.

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