INDICATIONS

Crohn's Disease
REMICADE® 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.

Pediatric Crohn's Disease
REMICADE® 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.

Ulcerative Colitis
REMICADE® 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.

Pediatric Ulcerative Colitis
REMICADE® 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.

Rheumatoid Arthritis
REMICADE®, 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).

Ankylosing Spondylitis
REMICADE® is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS).

Psoriatic Arthritis
REMICADE® 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).

Plaque Psoriasis
REMICADE® 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. REMICADE® should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.

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, blastomycosis, pneumocystosis, and cryptococcosis. Patients may present with disseminated, rather than localized, disease. 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, including Legionella, Listeria, and Salmonella.**

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, who are on treatment for latent TB, or who were previously treated for TB infection.

Risk of infection may be higher in patients greater than 65 years of age, pediatric patients, patients with co-morbid conditions and/or patients taking concomitant immunosuppressant 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. The majority of reported REMICADE® cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males. Almost 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 blockers, 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 blockers, 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 blockers 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).

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocker therapy, including REMICADE®. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

A population-based retrospective cohort study found a 2- to 3-fold increase in the incidence of invasive cervical cancer in women with rheumatoid arthritis treated with REMICADE® compared to biologics-naïve patients or the general population, particularly those over 60 years of age. A causal relationship between REMICADE® and cervical cancer cannot be excluded. Periodic screening should continue in women treated with REMICADE®.

CONTRAINDICATIONS

The use of REMICADE® at doses >5 mg/kg is contraindicated in patients with moderate or severe heart failure. REMICADE® is contraindicated in patients with a previous severe hypersensitivity reaction to infliximab or any of the inactive ingredients of REMICADE® or any murine proteins (severe hypersensitivity reactions have included anaphylaxis, hypotension, and serum sickness).

HEPATITIS B REACTIVATION

TNF blockers, including REMICADE®, have been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases were fatal. Patients should be tested for HBV infection before initiating REMICADE®. For patients who test positive, consult a physician with expertise in the treatment of hepatitis B. Exercise caution when prescribing 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 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 (eg, ≥5 times the upper limit of normal) develop, REMICADE® should be discontinued, and a thorough investigation of the abnormality should be undertaken.

HEART FAILURE

In a randomized, placebo-controlled study in patients with moderate or severe heart failure (NYHA Functional Class III/IV), higher mortality rates and a higher risk of hospitalization were

observed at Week 28 at a dose of 10 mg/kg and higher rates of cardiovascular events were observed at both 5 mg/kg and 10 mg/kg. There have been postmarketing reports of new onset and worsening heart failure, with and without identifiable precipitating factors. Patients with moderate or severe heart failure taking REMICADE® (≤5 mg/kg) or patients with mild heart failure should be closely monitored and treatment should be discontinued if new or worsening symptoms appear.

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. Anaphylaxis, acute urticaria, dyspnea, and hypotension have occurred in association with infusions of REMICADE®. Medications for the treatment of hypersensitivity reactions should be available.

CARDIOVASCULAR AND CEREBROVASCULAR REACTIONS DURING AND AFTER INFUSION
Serious cerebrovascular accidents, myocardial ischemia/infarction (some fatal), hypotension, hypertension, and arrhythmias have been reported during and within 24 hours of initiation of REMICADE® infusion. Cases of transient visual loss have been reported during or within 2 hours of REMICADE® infusion. Monitor patients during infusion and if a serious reaction occurs, discontinue infusion. Manage reactions according to signs and symptoms.

NEUROLOGIC EVENTS
TNF blockers, including REMICADE®, have been associated 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.

CONCURRENT ADMINISTRATION WITH OTHER BIOLOGICS
Concurrent use of REMICADE® with anakinra, abatacept, tocilizumab, or other biologics used to treat the same conditions as REMICADE® is not recommended because of the possibility of an increased risk of infection. 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 in the development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

VACCINATIONS AND USE OF LIVE VACCINES/THERAPEUTIC INFECTIOUS AGENTS

Prior to initiating REMICADE®, update vaccinations in accordance with current vaccination guidelines. Live vaccines or therapeutic infectious agents should not be given with REMICADE® due to the possibility of clinical infections, including disseminated infections.

At least a 6-month waiting period following birth is recommended before the administration of any live vaccine to infants exposed *in utero* to REMICADE®.

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

For more information, please see the full Prescribing Information and Medication Guide for REMICADE®. Provide the Medication Guide to your patients and encourage discussion.

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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