

REMICADE® (infliximab)

(*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 TNF α -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 TNF α -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 aminosaliclates. 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 aminosaliclates. **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 TNF α 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 TNF α . 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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FDA: Silicone Breast Implants Seem Safe

Implant use does not appear to trigger connective tissue diseases or rheumatoid arthritis.

BY KERRI WACHTER

Preliminary safety data from post-marketing studies confirm that silicone gel-filled breast implants are safe and effective when used as intended, but women should fully understand the risks prior to considering the implants.

The data come from a report released by the Food and Drug Administration that updates the clinical and scientific information for silicone implants.

"Our review ... continues to support the safety and effectiveness of silicone gel-filled implants when used as intended," Dr. Jeffrey Shuren, director of FDA's Center for Devices and Radiological Health, said in a press briefing. "We also want women to fully understand the risks and complications associated with these implants prior to considering them for breast augmentation or reconstruction."

As part of the FDA's November 2006 approval of two silicone gel-filled breast implants (the Allergan Natrelle and the Mentor MemoryGel), each manufacturer was required to conduct postapproval studies to characterize the long-term performance and safety of the devices.

In January 2011, the agency issued a statement about a possible but small association between silicone implants and anaplastic large cell lymphoma (ALCL).

The FDA's new "Update on the Safety of Silicone Gel-Filled Breast Implants" provides a clinical update on the two silicone gel-filled breast implants available in the United States.

The updated information includes preliminary data from the postapproval studies, a summary and analysis of adverse events reported to the FDA since approval, and a review and analysis of recent clinical publications about the safety and effectiveness of silicone gel-filled breast implants.

"I do want to emphasize today [that these data are] preliminary and that there are many more years of data collection needed to complete the required 10-year studies," said Dr. Shuren.

The report is not intended to provide a comprehensive clinical update about the safety of saline-filled breast implants.

Based on this report, according to the FDA news release, women should know the following:

► **Breast implants are not lifetime devices.** The longer a woman has silicone gel-filled breast implants, the more likely she is to experience complications. One in five patients who receive implants for breast augmentation will need them removed within 10 years.

For patients who receive implants for breast reconstruction, as many as one in two will require removal 10 years after implantation.

► **The most frequently observed complications and outcomes are capsular contracture (hardening of the area around the implant), reoperation (additional surgeries), and implant removal.** Other common complications include implant rupture, wrinkling, asymmetry, scarring, pain, and infection.

► **The complications that existed for women who received breast implants at the time of approval are similar to the complications observed today.**

► **Preliminary data do not indicate that silicone gel-filled breast implants cause breast cancer, reproductive problems, or connective tissue disease, such as rheumatoid arthritis.** However, in order to rule out these and other rare complications, studies would need to enroll more women and be longer in duration than those conducted thus far.

The FDA will be holding an expert advisory panel in the next few months to discuss how postapproval studies on breast implants can be more effective. For now, the agency is recommending that health care professionals and women who have silicone gel-filled breast implants do the following:

► **Follow up.** Women should continue to routinely follow up with their health care professionals. This includes getting routine MRIs to detect silent rupture. Dr. Shuren noted that the first MRI should occur at 3 years post implantation and every 2 years after that.

► **Be aware.** Breast implants are not lifetime devices. Breast implants are associated with significant local complications and outcomes, including capsular contracture, reoperation, removal, and implant rupture. Some women also experience breast pain, wrinkling, asymmetry, scarring, and infection.

► **Pay attention to changes.** Women should notify their health care professionals if they develop any unusual symptoms. All serious side effects should be reported to the breast implant manufacturer and to Medwatch, the FDA's safety information and adverse event reporting program.

► **Stay in touch.** If a woman has enrolled in a manufacturer-sponsored postapproval study, she should continue to participate.

These studies are the best way to collect information about the long-term rates of complications.

The agency also redesigned its website to include comprehensive information on silicone gel-filled and saline-filled breast implants. ■