

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 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 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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Analgesic Combination May Increase GI Bleeding

BY DOUG BRUNK

FROM ANNALS OF THE RHEUMATIC DISEASES

Combining ibuprofen and paracetamol at nonprescription doses conferred a modest improvement in pain relief in adults with knee pain/osteoarthritis. But this gain came at the expense of an increase in presumed gastrointestinal bleeding, results from a large randomized, controlled trial demonstrated.

The trial found that paracetamol 3 g per day may cause similar levels of blood loss as ibuprofen 1,200 mg per day, and that the combination of the two appears to be additive, or even synergistic in terms of the number of individuals with a decrease in hemoglobin greater than 2 g/dL.

“These results need to be confirmed, along with their clinical relevance and identification of the site of gastrointestinal bleeding,” wrote the researchers, who were led by Dr. Michael Doherty of the Arthritis UK Pain Center at Nottingham (England) City Hospital. “If confirmed, this observation should lead to the re-consideration of current recommendations for oral analgesic use in osteoarthritis and in chronic pain in general, and to the consideration of strategies to reduce this side effect.”

Over a period of 13 weeks, Dr. Doherty and his associates followed 892 adults with chronic knee pain who were randomized to one of four treatment regimens, each taken three times a day: ibuprofen (400 mg), paracetamol (1,000 mg), one fixed-dose combination tablet (ibuprofen 200 mg/paracetamol 500 mg), or two fixed-dose combination tablets (ibuprofen 400 mg/paracetamol 1,000 mg).

The primary short-term efficacy end point was the difference at 10 days between groups in the WOMAC (Western Ontario McMaster Universities) osteoarthritis index pain subscale, which was normalized to a 0- to 100-mm scale.

The primary long-term efficacy end point was the patient global assessment of study medication after 13 weeks. This was determined by asking patients, “Taking into account both how your medicine worked for you and any side effects you think it caused you, how would you rate your medication as a treatment for your painful knee?” Respondents used a 5-point scale for replies (1, excellent; 2, good; 3, fair; 4, poor; 5, unacceptable).

The primary safety end point was incidence of moderate and severe adverse

events reported during the study period (Ann. Rheum. Dis. 2011;70:1534-41).

Criteria for inclusion were age of at least 40 years; knee pain for most of the past 3 months and on 4 of 7 preceding days; discontinuation of current analgesics; Steinbrocker functional capaci-

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Major Finding: Combining ibuprofen and paracetamol at nonprescription doses conferred a modest improvement in pain relief after 10 days in adults with knee pain/osteoarthritis (P less than .01), but at the expense of an increase in presumed GI bleeding at 13 weeks.

Data Source: A study of 892 adults with chronic knee pain who were randomized to one of four treatment regimens, each taken three times a day.

Disclosures: The study was sponsored by Reckitt Benckiser Healthcare International Ltd. Dr. Doherty disclosed that he has received honoraria for attending two advisory boards for Reckitt Benckiser. In addition, one of the study authors is currently employed by the company and two others are former employees.

ty class I-III; and pain affecting the index knee (after a washout period if currently taking analgesics) of 30 mm or greater and 80 mm or less on a 100-mm visual analog scale over the previous 48 hours for one or more of the following: walking on a flat surface, going up/down stairs, at night, sitting, lying, or standing upright.

The mean age of patients was 61 years and 51% were men. More than half of the study participants (63%) had radiographic osteoarthritis, and 85% fulfilled American College of Rheumatology criteria for the condition.

After measuring the mean change in WOMAC pain scores from baseline, the researchers found that at day 10, two combination tablets provided significantly more pain relief, compared with paracetamol alone (P less than .01). At 13 weeks, a significantly greater proportion of participants taking one or two combination tablets rated their treatment as excellent/good, compared with paracetamol alone (P = .015 and .0002, respectively).

The incidence of adverse events was comparable among groups and consisted mainly of dyspepsia, diarrhea, and nausea. However, at 13 weeks a decrease in hemoglobin level by at least 1 g/dL was observed among some participants in all treatment groups. More than two-thirds of patients taking two combination tablets experienced this decrease (38%), compared with 24% taking one combination tablet, 20% taking paracetamol monotherapy, and 20% taking ibuprofen monotherapy.

At 13 weeks, a significantly greater proportion of patients in the two combination tablet group experienced a decrease in hemoglobin level by 2 g/L or greater (6.9%), compared with their counterparts in the one combination tablet (1.8%), paracetamol (0.9%), and ibuprofen (0.9%) treatment groups. ■