

REMICADE® (infliximab)

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**: 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*]. 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 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: Anakinra**: Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF α -blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF α -blocking agents. Therefore, the combination of REMICADE and anakinra is not recommended [see *Warnings and Precautions*]. **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 α analog 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 (5.7) and Adverse Reactions, Immunogenicity (6.1)*]. 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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IMPLEMENTING HEALTH REFORM

Medical Malpractice

Physicians have long sought an overhaul of the nation's tort system in the hope of reducing the financial and emotional costs involved with medical malpractice. The Affordable Care Act took a small step by funding demonstration projects to develop litigation alternatives. The law provides \$50 million to states for 5-year grants in fiscal year 2011, which began on Oct. 1, 2010. The Obama administration said it will give preference to states that develop programs that improve access to liability insurance and improve patient safety by reducing medical errors.

Dr. Albert L. Strunk, deputy executive vice president of the American College of Obstetricians and Gynecologists, discusses the current malpractice environment and the impact of health reform.



RHEUMATOLOGY

NEWS: Does

ACOG consider this proposal a step in the right direction?

Dr. Strunk: Any step that reduces the cost of litigation and improve determinations of good vs. bad medical care is a good idea. Whether you think medically related litigation costs \$11 billion or \$60 billion a year, the figures are substantial, so we're anxious to have trial or pilot programs go forward. We are grateful for any impact from the Affordable Care Act, but I think that real innovation also is occurring apart from the grants. There is increasing awareness that the way in which less-than-optimal outcomes occur requires attention to a constellation of factors; personnel is only one element. And we accept the notion that we have to pull ourselves up by our own bootstraps: While the 112th Congress may be more receptive to tort reform, we have to look to the states for legislative solutions.

RN: Some studies have suggested that the cost of medical malpractice is a fraction of overall health spending, and that tort reform would do little to bring down total health spending. How does the cost of medical malpractice impact the practice of ob.gyns.?

Dr. Strunk: In ob.gyn., tort awards are attached to neurologically impaired or neonatal encephalopathy types of cases, which allege primarily economic damages based on the life-care of an impaired infant, so reforms involving caps on noneconomic damages are of little assistance.

In addition, there has been a good deal of judicial nullification of statutes of limitations in cases involving infants. So obstetricians today face a practice environment whereby simply being at the wrong place at the wrong time can lit-

erally cause economic ruin. Surveys tell us that anxiety associated with this risk – as well as the cost and availability of liability insurance – influences the behavior of ob.gyns., and causes our physicians to leave obstetrics in their 40s (a significant impact on the workforce), all adding to our total health bill.

RN: Is ACOG working to reform tort laws at the state level?

Dr. Strunk: We are. Most state initiatives relate to traditional California MICRA (Medical Injury Compensation Reform Act)-style tort reform, addressing noneconomic damages through caps, as well as limiting contingency fees. The most successful initiative has been in Texas, where the impact of the cap on noneconomic damages – coupled with a constitutional amendment that

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prevented the courts from overturning the legislation – has resulted in a huge influx of doctors. Access to care, particularly in low-income populations, has been dramatically increased.

In the short term, caps on noneconomic damages are helpful in selected state environments. Some states are exploring a contractual arrangement between patient and physician for pre-dispute voluntary binding arbitration. Another long-term goal would be the implementation of health courts.

RN: What would ACOG ideally like to see happen with the malpractice reform demonstration projects?

Dr. Strunk: We are very supportive of a project grant in Missouri, which is going to focus on the quality of perinatal care and the way adverse perinatal events are managed in five Missouri hospitals. They are going to establish an evidence-based obstetrics practice model. We believe that the use of evidence-based guidelines and checklists increases patient safety and reduces risk.

The Carilion Roanoke Memorial Hospital Center has a planning grant to enhance teamwork and systems management, the goal being to improve the quality of obstetrical and patient care and reduce risk and liability. Team-based care, systems analysis, and systems solutions are essential. Most mishaps that occur in the delivery of care don't really relate to the negligence of a single person, notwithstanding what the tort system would have us believe. It is generally a constellation of factors.

So these are things we are not merely supportive of, but also enthusiastic about.

DR. STRUNK is also the vice president for fellowship activities at ACOG.