

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 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 (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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Three Provisos Guide Contract Negotiation

BY SALLY KOCH KUBETIN

EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

ATLANTA – Following three basic rules can help you to avoid taking misleading employment offers that can hound you – and cost you – for years to come, Joan M. Roediger told newly minted rheumatology fellows during a special session at the annual meeting of the American College of Rheumatology.

Ms. Roediger's "three basic rules of employment contracts" are:

- ▶ It should never cost money to take a job.
- ▶ It should never cost you anything to work in a job.
- ▶ It should never cost you anything to leave a job.

Ms. Roediger, an attorney and partner at the firm of Obermayer, Rebmann, Maxwell & Hippel LLP in Philadelphia, said "the best contract you sign is one you put in a drawer and never look at again. The contract is for when something goes wrong."

But often something does go wrong, she said. More than 60% of young physicians change jobs within the first 2-3 years of employment.

Further, she acknowledged that the shortcomings of some contracts are not readily apparent. Often, what is not mentioned in the contract is problematic.

The first document signed in the process of getting hired is the letter of intent. Do not sign and return it without reading it carefully, she said. First, one should look out for terms that seem unfair: a too-low salary, too much on-call time, not enough leave. Also, make sure the letter of intent contains the wording that it is "not legally binding."

Hospital assistance agreements – which may be known as income guarantee, recruitment, or loan agreements – are part of the private practice hiring process in underserved areas. The community hospital assists the private practice in bringing the hired physician into the community. Salary is guaranteed for a period of time, and other incentives are paid by the hospital. These agreements are filled with pitfalls, she said. "The one time I would insist you

hire a lawyer is when you are faced with both a hospital income agreement and an employment agreement."

Ms. Roediger also offered the following general recommendations about contract negotiation:

▶ **Get moving expenses covered.** "I feel very firmly that moving expenses should be paid, whether I am representing the employer or employee. And they should not be paltry. Your days of hiring a rental truck and hauling your own sofas are over. Call a mover for an estimate." Expenses should be paid at the time of the move, or better yet, have the mover bill the employer directly.

▶ **Ask for a signing bonus.** "If you don't ask for one, you are not going to be given one. At this point in your career, you can expect anything from between \$5,000 and \$25,000." The signing bonus should be paid at signing. There is a disturbing trend for it to be paid in thirds starting 90 days after the signing, she said.

▶ **Avoid payback stipulations.** If you leave the job, you should not have to pay back moving expenses. In an ideal world, signing bonuses should not have to be repaid. But Ms. Roediger said that she will accept that a physician who quits within the first year can be asked to pay back a prorated amount.

Under poorly negotiated hospital income agreements, if the physician does not stay in the community for the contracted period of time, he/she may have to pay back all the money. In fact, the practice rather than the physician is the entity that benefited from the agreement, she said.

Beware of contracts that require that things like continuing medical education allowance, hospital dues, or used vacation time be paid back on a prorated basis if the physician leaves before the end of the contract.

▶ **Get a guarantee of income.** Employment agreements without a guarantee of income are unusual, but she has seen a few, mostly in the Atlanta and the Washington metro regions, said Ms. Roediger.

Under such terms, known as "eat what you kill," one might as well be a solo practitioner, she said.

Ms. Roediger disclosed no conflicts of interest. ■

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