

## POLICY & PRACTICE

### House Passes Arthritis Bill

Landmark arthritis legislation that would establish a National Arthritis Action Program passed the House of Representatives just before it recessed for the general election. The Arthritis Prevention, Control, and Cure Act (H.R. 1283) would promote research into the control, prevention, and surveillance of arthritis and other rheumatic diseases. The legislation also would aim to increase the supply of pediatric rheumatologists in the United States by increasing the number and size of institutional training grants. Another part of the bill would create a loan repayment program in pediatric rheumatology. "The bill invests in the critical needs of those suffering from arthritis and in research that will help future generations of Americans who are diagnosed with the disease," Rep. Anna G. Eshoo (D-Calif.), sponsor of the legislation, said in a statement. A companion bill (S. 626) is pending before the Senate Committee on Health, Education, Labor, and Pensions.

### Florida Files Vioxx Suit

Florida Attorney General Bill McCollum has sued Merck & Co. on behalf of state agencies he said were damaged by "the company's allegedly deceptive marketing and promotion" of Vioxx. The lawsuit follows a 3-year investigation of Merck's practices in the promotion of Vioxx (rofecoxib) and alleges that, because of the company's marketing practices, numerous Florida agencies approved the inclusion of Vioxx as a covered or approved drug. Vioxx purchases by the Florida Medicaid program exceeded \$80 million between 1999 and 2004, according to McCollum, who argued that if the facts about Vioxx had been known earlier, physicians and their Medicaid patients would have chosen other, less expensive prescriptions. Eight other states have filed similar lawsuits, according to Merck spokesman Ronald Rogers, who said in an interview that Merck acted responsibly on Vioxx and will defend against the suits.

### Industry Groups Protest IVIg Cuts

The Biotechnology Industry Organization, the American Society of Clinical Oncology, the Association of Community Cancer Centers, and the Alliance for Plasma Therapies are urging the Centers for Medicare and Medicaid Services to preserve the preadministration fee currently paid for administering intravenous immune globulin (IVIg) therapy in hospital outpatient settings. The CMS proposed to eliminate the payment as part of its hospital outpatient prospective

payment system rule for next year, which was published in July. The preadministration payment began in 2006 at a time when IVIg supplies were tight, driving up the price. CMS officials say it's not clear that supply is still an issue, but manufacturers and patient organizations say there are still difficulties. "BIO does not believe that there is stability in the [IVIg] marketplace when over 40% of the providers cannot purchase [IVIg] at or below the Medicare payment rate," said the group in its comments. The CMS also said that it wants to cut the add-on fee because IVIg use has gone up markedly. BIO argued that increased use shows that the preadministration payment has helped providers acquire and administer the drug.

### GAO: FDA Needed Broader Pool

Food and Drug Administration officials might have avoided some conflicts of interest on their scientific advisory committees by expanding recruitment efforts beyond word-of-mouth nominations, according to a report from the Government Accountability Office. The report, released last month, analyzed the recruitment and screening of FDA advisory committee members before the agency changed those processes in 2007. The FDA could have reached out beyond its usual source of experts to retired professionals, university professors, and experts in epidemiology and statistics, the GAO concluded. The evaluation was requested by members of the Senate.

### Nationwide RAC Launched

The CMS has launched its national recovery audit contractor program as part of its "aggressive new steps to find and prevent waste, fraud and abuse in Medicare." The new RACs, which will be paid on a contingency fee basis, soon will begin to contact providers, the CMS said. The 3-year RAC demonstration program in California, Florida, New York, Massachusetts, South Carolina, and Arizona collected more than \$900 million in overpayments, according to the agency. But the program has drawn strong criticism from physician groups, who have maintained that RAC audits were overly burdensome. In addition to implementing the RACs, the CMS said it will begin to work directly with beneficiaries to make certain that they receive the durable medical equipment or home health services for which Medicare has been billed, and that the items or services were medically necessary.

—Mary Ellen Schneider

Table 10:  
Percent of RA Patients Reporting Adverse Events  
in Controlled Clinical Trials\*

| Event                                       | Placebo Controlled                |                                  | Active Controlled (Study III) |                     |
|---|-----------------------------------|----------------------------------|-------------------------------|---------------------|
|   | Placebo <sup>†</sup><br>(N = 152) | ENBREL <sup>†</sup><br>(N = 349) | MTX<br>(N = 217)              | ENBREL<br>(N = 415) |
| Injection site reaction                     | 10                                | 37                               | 7                             | 34                  |
| Infection (total)**                         | 32                                | 35                               | 72                            | 64                  |
| Non-upper respiratory infection (non-URI)** | 32                                | 38                               | 60                            | 51                  |
| Upper respiratory infection (URI)**         | 16                                | 29                               | 39                            | 31                  |
| Headache                                    | 13                                | 17                               | 27                            | 24                  |
| Nausea                                      | 10                                | 9                                | 29                            | 15                  |
| Rhinitis                                    | 8                                 | 12                               | 14                            | 16                  |
| Dizziness                                   | 5                                 | 7                                | 11                            | 8                   |
| Pharyngitis                                 | 5                                 | 7                                | 9                             | 6                   |
| Cough                                       | 3                                 | 6                                | 6                             | 5                   |
| Asthenia                                    | 3                                 | 5                                | 12                            | 11                  |
| Abdominal pain                              | 3                                 | 5                                | 10                            | 10                  |
| Rash  | 3                                 | 5                                | 23                            | 14                  |
| Peripheral edema                            | 3                                 | 2                                | 4                             | 8                   |
| Respiratory disorder                        | 1                                 | 5                                | NA                            | NA                  |
| Dyspepsia                                   | 1                                 | 4                                | 10                            | 11                  |
| Sinusitis                                   | 2                                 | 3                                | 3                             | 5                   |
| Vomiting                                    | -                                 | 3                                | 8                             | 5                   |
| Mouth ulcer                                 | 1                                 | 2                                | 14                            | 6                   |
| Alopecia                                    | 1                                 | 1                                | 12                            | 6                   |
| Pneumonitis ("MTX lung")                    | -                                 | -                                | 2                             | 0                   |

\* Includes data from the 6-month study in which patients received concurrent MTX therapy.

<sup>†</sup> The duration of exposure for patients receiving placebo was less than the ENBREL-treated patients.

\*\* Infection (total) includes data from all three placebo-controlled trials. Non-URI and URI include data only from the two placebo-controlled trials where infections were collected separately from adverse events (placebo N = 110, ENBREL N = 213).

In controlled trials of RA and psoriatic arthritis, rates of serious adverse events were seen at a frequency of approximately 5% among ENBREL- and control-treated patients. In controlled trials of plaque psoriasis, rates of serious adverse events were seen at a frequency of < 1.5% among ENBREL- and placebo-treated patients in the first 3 months of treatment. Among patients with RA in placebo-controlled, active-controlled, and open-label trials of ENBREL, malignancies (see **WARNINGS: Malignancies**, **ADVERSE REACTIONS: Malignancies**) and infections (see **ADVERSE REACTIONS: Infections**) were the most common serious adverse events observed. Other infrequent serious adverse events observed in RA, psoriatic arthritis, ankylosing spondylitis, or plaque psoriasis clinical trials are listed by body system below:

**Cardiovascular:** heart failure, myocardial infarction, myocardial ischemia, hypertension, hypotension, deep vein thrombosis, thrombophlebitis  
**Digestive:** cholecystitis, pancreatitis, gastrointestinal hemorrhage, appendicitis  
**Hematologic/Lymphatic:** lymphadenopathy  
**Musculoskeletal:** bursitis, polymyositis  
**Nervous:** cerebral ischemia, depression, multiple sclerosis (see **WARNINGS: Neurologic Events**)  
**Respiratory:** dyspnea, pulmonary embolism, sarcoidosis  
**Skin:** worsening psoriasis  
**Urogenital:** membranous glomerulonephropathy, kidney calculus

In a randomized controlled trial in which 51 patients with RA received ENBREL 50 mg twice weekly and 25 patients received ENBREL 25 mg twice weekly, the following serious adverse events were observed in the 50 mg twice weekly arm: gastrointestinal bleeding, normal pressure hydrocephalus, seizure, and stroke. No serious adverse events were observed in the 25 mg arm.

#### Adverse Reactions in Patients with JIA

In general, the adverse events in pediatric patients were similar in frequency and type as those seen in adult patients (see **WARNINGS** and other sections under **ADVERSE REACTIONS**). Differences from adults and other special considerations are discussed in the following paragraphs. Severe adverse reactions reported in 69 JIA patients ages 4 to 17 years included varicella (see also **PRECAUTIONS: Immunizations**), gastroenteritis, depression/personality disorder, cutaneous ulcer, esophagitis/gastritis, group A streptococcal septic shock, Type 1 diabetes mellitus, and soft tissue and post-operative wound infection.

Forty-three of 69 (62%) children with JIA experienced an infection while receiving ENBREL during three months of study (part 1 open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types of infections reported in JIA patients were generally mild and consistent with those commonly seen in outpatient pediatric populations. Two JIA patients developed varicella infection and signs and symptoms of aseptic meningitis which resolved without sequelae.

The following adverse events were reported more commonly in 69 JIA patients receiving 3 months of ENBREL compared to the 349 adult RA patients in placebo-controlled trials. These included headache (19% of patients, 1.7 events per patient-year), nausea (9%, 1.0 events per patient-year), abdominal pain (19%, 0.74 events per patient-year), and vomiting (13%, 0.74 events per patient-year).

In open-label clinical studies of children with JIA, adverse events reported in those aged 2 to 4 years were similar to adverse events reported in older children.

In post-marketing experience, the following additional serious adverse events have been reported in pediatric patients: abscess with bacteremia, optic neuritis, pancytopenia, seizures, tuberculous arthritis, urinary tract infection (see **WARNINGS**), coagulopathy, cutaneous vasculitis, and transaminase elevations. The frequency of these events and their causal relationship to ENBREL therapy are unknown.

#### Patients with Heart Failure

Two randomized placebo-controlled studies have been performed in patients with CHF. In one study, patients received either ENBREL 25 mg twice weekly, 25 mg three times weekly, or placebo. In a second study, patients received either ENBREL 25 mg once weekly, 25 mg twice weekly, or placebo. Results of the first study suggested higher mortality in patients treated with ENBREL at either schedule compared to placebo. Results of the second study did not corroborate these observations. Analyses did not identify specific factors associated with increased risk of adverse outcomes in heart failure patients treated with ENBREL (see **PRECAUTIONS: Patients with Heart Failure**).

#### Adverse Reaction Information from Spontaneous Reports

Adverse events have been reported during post-approval use of ENBREL. 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 ENBREL exposure.

Additional adverse events are listed by body system below:

**Body as a whole:** angioedema, fatigue, fever, flu syndrome, generalized pain, weight gain  
**Cardiovascular:** chest pain, vasodilation (flushing), new-onset congestive heart failure (see **PRECAUTIONS: Patients with Heart Failure**)  
**Digestive:** altered sense of taste, anorexia, diarrhea, dry mouth, intestinal perforation  
**Hematologic/Lymphatic:** adenopathy, anemia, aplastic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia (see **WARNINGS**)  
**Hepatobiliary:** autoimmune hepatitis  
**Musculoskeletal:** joint pain, lupus-like syndrome with manifestations including rash consistent with subacute or discoid lupus  
**Nervous:** paresthesias, stroke, seizures, and central nervous system events suggestive of multiple sclerosis or isolated demyelinating conditions such as transverse myelitis or optic neuritis (see **WARNINGS**)  
**Ocular:** dry eyes, ocular inflammation  
**Respiratory:** dyspnea, interstitial lung disease, pulmonary disease, worsening of prior lung disorder  
**Skin:** cutaneous vasculitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, pruritus, subcutaneous nodules, urticaria

**Rx Only. This brief summary is based on ENBREL prescribing information v. 33: 03/2008**

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