# Crohn Disease Drug Backed, With Restrictions

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GAITHERSBURG, MD. — A federal advisory panel has recommended that the immune modulator natalizumab be approved to treat moderate to severe Crohn disease under highly restrictive conditions.

Because of the serious risks associated with this agent, including progressive multifocal leukoencephalopathy (PML) and other opportunistic infections, the panel recommended that natalizumab use be restricted to those who have failed other treatments or cannot tolerate anti–tumor necrosis factor therapies.

At a joint meeting, the Food and Drug Administration's Gastrointestinal Drugs and Drug Safety and Risk Management advisory committees voted 12-3, with 2 abstentions, in favor of approving natalizumab for this indication. The FDA usually follows the recommendations of its advisory panels, which are not binding.

The chairman of the GI drugs panel, Dr. David B. Sachar, said that he supported approval for patients with moderate to severe Crohn who have evidence of ongoing inflammation, such as an elevated C-reactive protein (CRP) level, and "who have failed to achieve adequate sustained responses to safe and well-tolerated medications, steroids, and immunomodulators." Anti-TNF therapies and immunomodulators should be discontinued before starting treatment, he said. Natalizumab should be discontinued if the patient has not responded in 3 months or if steroids cannot be discontinued within 6 months of starting treatment, added Dr. Sachar, director emeritus of the division of gastroenterology, Mount Sinai School of Medicine, New York.

Dr. Robert Levine, professor of medicine in the division of gastroenterology, State University of New York, Syracuse, said that while it was clear this drug was "no blockbuster," he would support its availability with a new mechanism of action for this population, with a risk management plan that was as restrictive as possible.

Those voting against approval expressed concerns about the unknown long-term risks of natalizumab in Crohn patients.

Natalizumab, marketed as Tysabri by Elan Pharmaceuticals Inc. and Biogen Idec, is administered in a monthly infusion, and is approved as monotherapy for treating relapsing forms of multiple sclerosis. It is available through the TOUCH program, a risk management plan that was developed to address the risk of PML, a rare but usually fatal, progressive demyelinating CNS infection that was reported in three patients treated with natalizumab in trials. Two cases, one of which was fatal, were identified soon after natalizumab was initially approved to treat MS in November 2004. These cases prompted the manufacturer to take natalizumab off the market and suspend clinical trials in February 2005.

A fatal case of PML subsequently was identified in a 60-year-old man who had received a total of 8 months of natalizumab treatment in the Crohn disease trial; the man had a history of immunosuppressant use and lymphopenia. The TOUCH program was initiated when natalizumab was reintroduced to the U.S. market in June 2006.

PML is caused by activation of a human polyomavirus—the JC virus—which is latent in many healthy adults but can be activated in people who are immunosuppressed. The two MS patients with PML also were being treated with interferon beta-1a; when natalizumab was reintroduced, it was approved as monotherapy.

Components of the TOUCH program include a mandatory registry of patients and physicians, centralized distribution of the product, a monthly preinfusion checklist to screen patients for new or worsening symptoms that could indicate PML and use of immunosuppressants, and mandatory reporting of PML cases.

To date, no other PML cases have been identified in MS patients who have received natalizumab under the restricted program, and the risk of PML currently is estimated at about 1/1,000 patients treated with natalizumab for a mean of 18 months. The risk with longer treatment is not known.

Natalizumab was compared with placebo in two induction studies of 1,415 patients with moderately to severely active Crohn disease, and a 12-month maintenance study, which evaluated 300 mg of natalizumab administered intravenously every 4 weeks, the currently approved regimen for MS. In these trials, the beneficial effects over placebo were modest, and not as striking as in the MS studies. Patients

were allowed to continue using 5-aminosalicylic acid, steroids, and immunosuppressants, but not anti-TNF therapy.

In the first induction study, the clinical response rate—a reduction in the Crohn's Disease Activity Index (CDAI) score of at least 70 from baseline—was not significantly different at 10 weeks between the 724 patients on natalizumab and the 181 patients on placebo (56% vs. 49%).

In a post hoc analysis of patients in the trial who had an elevated CRP, response rates were 58% among those on natalizumab vs. 45% among those on placebo, a significant difference.

In the second induction study of more than 500 patients, only those with elevated CRP levels were enrolled to determine whether the effectiveness of natalizumab was greater when inflammation was increased, as measured by an elevated CRP. At weeks 8 and 12, clinical response rates were significantly higher among those on natalizumab than placebo (48% vs. 32%), a statistically significant difference.

In the maintenance study that enrolled responders to natalizumab to placebo or natalizumab, response rates at 9 and 15 months were 61% and 54%, respectively, among those who continued on natalizumab vs. 28% and 20%, among those on placebo, significant differences.

No PML cases were identified in the studies. Adverse events included hypersensitivity reactions, at a rate of 3.5%. The malignancy rate was slightly higher for natalizumab vs. placebo (0.6% vs. 0.2%). Infections were slightly more common, including upper respiratory tract infections and herpes simplex infections, in natalizumab-treated patients. There were two cases of viral meningitis and one case of cytomegalovirus colitis, but none in placebo-treated patients in the 3-month trials.

The company has proposed a version of the TOUCH prescribing program adapted for Crohn disease patients, called "CD-TOUCH," with the same goals but with modifications to accommodate differences in the treatment and management of patients with CD. One difference is the recommendation to stop treatment in patients who have had no response in 3 months and to eliminate corticosteroid use within 6 months of starting treatment.

As of July 2007, more than 8,600 patients had received treatment with natalizumab commercially, and more than 4,300 patients were receiving the drug in the European Union. In July, Elan and Biogen Idec announced that they were appealing a European Medicines Agency decision against approving natalizumab for patients with Crohn disease. ■