



## Notification of Product Approval

The Division of Division of Gastroenterology Products would like to inform you of a recent new drug approval or update to the labeling of an approved drug. See below for a summary of the drug's approved use and any significant safety issues. The full prescribing information for this drug is attached and will also be posted on the Center for Drug Evaluation and Research (CDER) internet web site under "Drug Information" (<http://www.fda.gov/cder/drug/default.htm>).

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Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
Food and Drug Administration

PRODUCT NAME: Tysabri (Natalizumab) Injection  
APPROVAL DATE: January 14, 2008  
SPONSOR: Biogen Idec and Elan

\_\_\_\_\_ **New Product**

Indication:

Efficacy summary:

Safety summary:

X **New Indication**

Indication:

Tysabri is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF- $\alpha$ . Tysabri should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF- $\alpha$ .

Efficacy summary:

Three randomized, double-blind, placebo-controlled clinical trials were conducted in 1414 adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI]  $\geq 220$  and  $\leq 450$ ). Concomitant inhibitors of TNF- $\alpha$  were not permitted. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunosuppressants (e.g., 6-mercaptopurine, azathioprine, or methotrexate) were permitted. Overall, approximately two-thirds of patients were not taking concomitant immunosuppressants, and approximately one-third of patients were taking neither concomitant immunosuppressants nor concomitant corticosteroids.

Induction of clinical response (defined as  $\geq 70$ -point decrease in CDAI from baseline) was evaluated in two studies, CD1 and CD2. In Study CD1, 896 patients were randomized 4:1 to receive three monthly infusions of either 300 mg Tysabri or placebo. At Week 10, 56% of the 717 patients receiving Tysabri were in response compared to 49% of the 179 patients receiving placebo (treatment effect: 7%; 95% confidence interval (CI): [-1%, 16%];  $p=0.067$ ). In a *post hoc* analysis of the subset of 653 patients with elevated baseline C-reactive protein (CRP), indicative of active inflammation, 57% of Tysabri patients were in response compared to 45% of those receiving placebo (treatment effect: 12%; 95% CI: [3%, 22%]; nominal  $p=0.01$ ). In the second induction trial, Study CD2, only patients with elevated serum CRP were studied. A total of 509 patients were randomized 1:1 to receive three monthly infusions of either 300 mg Tysabri or placebo. In Study CD2, in contrast to

Study CD1, clinical response and clinical remission (defined as CDAI score <150) were required to be met at both Weeks 8 and 12; results are shown below.

**Table 1.** Induction of Clinical Response and Remission in Study CD2

	TYSABRI n=259	Placebo n=250	Treatment Difference (95% CI)
Clinical Response at:			
Week 8	56%	40%	16% (8%, 26%)
Week 12	60%	44%	16% (7%, 25%)
Both Weeks 8 & 12*	48%	32%	16% (7%, 24%)
Clinical Remission at:			
Week 8	32%	21%	11% (3%, 19%)
Week 12	37%	25%	12% (4%, 21%)
Both Weeks 8 & 12*	26%	16%	10% (3%, 18%)

\*p < 0.005

Maintenance therapy was evaluated in Study CD3. In this study, 331 patients from Study CD1 that had had a clinical response to Tysabri at both Weeks 10 and 12 were re-randomized 1:1 to treatment with continuing monthly infusions of either 300 mg Tysabri or placebo. Maintenance of response was assessed by the proportion of patients who did not lose clinical response at any study visit for an additional 6 and 12 months of treatment (i.e., Month 9 and Month 15 after initial treatment with Tysabri). The study also assessed the proportion of patients who did not lose clinical remission at any study visit within the subset of those who were in remission at study entry. (See table below.)

**Table 2.** Maintenance of Clinical Response and Remission in Study CD3

	Tysabri	Placebo	Treatment Difference (95% CI)
Clinical Response through:	n=164	n=167	
Month 9*	61%	29%	32% (21%, 43%)
Month 15	54%	20%	34% (23%, 44%)
Clinical Remission through:	n=128 <sup>†</sup>	n=118 <sup>†</sup>	
Month 9*	45%	26%	19% (6%, 31%)
Month 15	40%	15%	25% (13%, 36%)

\*p < 0.005

<sup>†</sup>Number of patients included for analysis of “through” Month 9 and Month 15 includes only those in remission upon entry into Study CD3.

Response is defined as CDAI <220 and a ≥70-point reduction in CDAI score compared to Baseline from Study CD1. Remission is defined as CDAI <150.

In studies CD1, CD2, and CD3, for subgroups defined by prior use of, or by inadequate response to prior therapies (i.e., corticosteroids, immunosuppressants, and inhibitors of TNF-α), the treatment effect was generally similar to that seen in the whole study population. In the subgroup of patients that were taking neither concomitant immunosuppressants nor concomitant corticosteroids, the treatment effect was generally similar to that seen in the whole study population.

In the subgroup of patients (n=65) who were receiving corticosteroid medication at baseline, responded to Tysabri in Study CD1, and were re-randomized to Tysabri in Study CD3, approximately two-thirds were able to discontinue steroids within 10 weeks of initiating a steroid taper.

#### Safety summary:

Tysabri is only available through a special restricted distribution program called the TOUCH Prescribing Program. TOUCH was implemented to address the risk of progressive multifocal leukoencephalopathy (PML) associated with the use of Tysabri. Two cases of PML were observed in 1869 patients with multiple sclerosis treated for a median of 120 weeks; the third case occurred among 1043 patients with Crohn’s disease after the patient received eight doses. PML is caused by an opportunistic virus that infects the brain, usually leading to death or severe disability. Tysabri carries a boxed warning for PML. TOUCH is designed to minimize the risk of PML by ensuring appropriate use of Tysabri and appropriate monitoring of patients on Tysabri by health care providers. Patients, prescribers, pharmacies, and infusion centers must all be enrolled in the TOUCH Program and agree to

comply with its guidelines. Additionally, TOUCH requires prescribers, pharmacists, infusion center staff, and patients to participate in an extensive educational program about potential PML infection associated with Tysabri treatment and the requirements of the program. Both Biogen Idec and Elan have agreed to conduct safety surveillance, including monitoring and expedited reporting of PML infections, other serious opportunistic infections, malignancies, and deaths and systematic tracking of patients and drug disposition to FDA.

The following serious adverse events in the induction Studies CD1 and CD2 were reported more commonly with Tysabri than placebo and occurred at an incidence of at least 0.3%: intestinal obstruction or stenosis (2% vs. 1% in placebo), acute hypersensitivity reactions (0.5% vs. 0%), abdominal adhesions (0.3% vs. 0%), and cholelithiasis (0.3% vs. 0%). Similar serious adverse events were seen in the maintenance Study CD3.

In Studies CD1 and CD2, the rate of any type of infection was 1.7 per patient-year in Tysabri-treated patients and 1.4 per patient-year in placebo-treated patients. In Study CD3, the incidence of any type of infection was 1.7 per patient-year in Tysabri-treated patients and was similar in placebo-treated patients. The most common infections were nasopharyngitis, upper respiratory tract infection, and influenza. In Studies CD1 and CD2, the incidence of serious infection was approximately 2.1% in both Tysabri-treated patients and placebo-treated patients. In Study CD3, the incidence of serious infection was approximately 3.3% in Tysabri-treated patients and approximately 2.8% in placebo-treated patients. In clinical studies for CD, opportunistic infections (pneumocystis carinii pneumonia, pulmonary mycobacterium avium intracellulare, bronchopulmonary aspergillosis, and burkholderia cepacia) have been observed in <1% of Tysabri-treated patients; some of these patients were receiving concurrent immunosuppressants. Two serious non-bacterial meningitides occurred in Tysabri-treated patients compared to none in placebo-treated patients.

Infusion-related reactions more common in CD patients receiving Tysabri than those receiving placebo included headache, nausea, urticaria, pruritus, and flushing. Serious infusion reactions occurred in Studies CD1, CD2, and CD3 at an incidence of <1% in Tysabri-treated patients.

Clinically significant liver injury has been reported in patients treated with Tysabri in the postmarketing setting. Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as six days after the first dose; signs of liver injury have also been reported for the first time after multiple doses. In some patients, liver injury recurred upon rechallenge, providing evidence that Tysabri caused the injury.

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### **Significant safety update**

Safety summary:

Additional information about this product is available on CDER's web site at *(insert url)*.  
(Use only if a specific drug or biologic information web site is created for this product)