Biogen Idec and Elan Corporation announced today that their safety evaluation of Tysabri® (natalizumab) in patients with Crohn’s disease and rheumatoid arthritis is now complete. They reported finding no new confirmed cases of PML (progressive multifocal leukoencephalopathy, a rare and frequently fatal disease of the central nervous system) in those patients. They had previously announced having found no new cases of PML after completing the safety evaluation of Tysabri in MS.

On September 26, 2005 the companies announced that they had filed a supplemental Biologics License Application with the U.S. FDA for permission to reintroduce Tysabri to the market for treating relapsing MS.

The companies had voluntarily suspended the drug from the market in February following the diagnosis of two cases of PML in patients treated with Tysabri in combination with Avonex® (interferon beta-1a) in clinical trials for multiple sclerosis. One of these was fatal. A third case of PML was identified in a patient, who died in 2003, who had participated in a trial of Tysabri for Crohn’s disease. Details of these cases were published in *The New England Journal of Medicine*.

According to the sponsors, they have requested a priority review of their supplemental Biologics License Application (sBLA), which, if granted by the FDA, would result in FDA action within an estimated six months from the submission date, rather than the 10 months expected for a standard review. The sBLA includes final two-year data from the phase 3 AFFIRM and SENTINEL trials of Tysabri, along with the safety evaluation, revised labeling and a risk management plan.
It is expected, but not certain, that the FDA will convene an advisory panel of experts to evaluate the safety report and clinical trial results in order to make recommendations about the drug’s safety and the advisability of its return to the market.

“We look forward to seeing the full safety and efficacy data and to seeing the results of the FDA’s safety review,” said John R. Richert, MD, National MS Society Vice President of Research and Clinical Programs.

Further Information about the February suspension of Tysabri
See below for Questions and Answers about this situation.

The FDA issued a public health advisory to inform patients and health care providers about the suspended marketing of Tysabri. For more information from the FDA, including the public health advisory and questions and answers on the Tysabri suspension, go to: www.fda.gov/cder/drug/infopage/natalizumab

To access the companies’ letter to healthcare professionals, download: www.tysabri.com/hcp.pdf

Questions & Answers About the Marketing Suspension of Tysabri
(Updated October 17, 2005)

Q: What were the adverse events related to the suspension of Tysabri?
A: Three cases of PML have been diagnosed in people taking Tysabri in clinical trials. Two of these people have died.

Two individuals who were taking Tysabri and Avonex (interferon beta-1a) in combination experienced adverse events that led to the suspension of Tysabri. Two patients developed PML, one of whom died. The adverse events occurred after these individuals had completed participation in the SENTINEL trial (where people on Avonex began taking Tysabri as an add-on treatment), but were continuing therapy as part of an extension study. They had been taking the combination therapy for over two years.

One person, who died in 2003, had participated in a trial of Tysabri alone for Crohn’s disease. Prior medication history included multiple courses of immunosuppressant agents. In 2003, the case in the Crohn’s trial was reported by a clinical trial investigator as malignant astrocytoma, a diagnosis that was confirmed at the time by tissue analysis. Biogen Idec and Elan identified this case in the course of their evaluation of patients who were involved in clinical trials of Tysabri, and reassessed the diagnosis as PML.
Q: What is PML, and is it treatable?
A: According to the National Institutes of Health, progressive multifocal leukoencephalopathy is a rare, rapidly progressive disorder of the nervous system that is caused by a common virus, the “JC virus.” It usually occurs in persons who have severe immune-system suppression. Symptoms include mental deterioration, vision loss, speech disturbances, loss of coordination, paralysis, and ultimately coma and usually death. There is no cure for PML. However, improvement is sometimes seen when immune function is increased.

Q: Is there a test available that can predict that a person will develop PML?
A: At this time, there is no laboratory or other test available that can predict that a person will develop PML.

Q: Is the company reviewing all patients who have taken Tysabri for possible PML?
A: The companies have stated that they have completed their evaluation of patients who received treatment during the clinical trials of Tysabri. On August 9, 2005 they announced that the investigation of multiple sclerosis patients was completed. This investigation also included several suspected cases in persons who had taken the drug outside of clinical trials, and according to company spokespersons, none of these suspected cases in persons with MS were confirmed. On October 17, 2005 the companies announced that the safety evaluation in Crohn’s disease and rheumatoid arthritis patients was completed.

Q: What was entailed in the companies’ safety investigation involving persons with MS?
A: The clinical trial sites communicated with trial participants to let them know whether they received Tysabri or the placebo. According to company spokespersons, of over 2,000 patients with MS who had been enrolled in clinical trials and had been on Tysabri, 91% agreed to be evaluated as part of the safety investigation. Of those, 99% were seen by their neurologist and received a physical and neurological examination. Ninety-eight percent also had MRI scans. A smaller proportion of patients had spinal taps and their spinal fluid was evaluated for signs of the JC virus. Results of all of these examinations were evaluated for signs of PML.

Several reports of suspected cases of PML had been reported to the FDA after the suspension of Tysabri, and these cases were also evaluated by a panel of PML experts. No new cases of PML have been identified.
Q: How long will it take before we know whether Tysabri will be made available again?
A: The companies have stated that they have asked the FDA to conduct a “priority review” of the safety and clinical trials data provided. If the FDA agrees to a priority review, it would take about six months; if the FDA conducts a standard review, it should take about 10 months. It would be expected, but not certain, that the FDA would establish an advisory committee to evaluate the information in terms of safety, risks and benefits, and make recommendations about whether the drug should be returned to market. There is no way to predict whether or not the FDA will permit the return of Tysabri to the market.

Q: What can we tell people who have taken Tysabri and have concerns about their own safety?
A: In a Public Health Advisory issued February 28, 2005 (www.fda.gov/cder/drug/advisory/natalizumab.htm) the U.S. Food and Drug Administration suggests that patients who had been treated with Tysabri contact their physician to discuss appropriate evaluation and alternative treatments.

Q: Are people who were on Tysabri in danger of something happening even after they stop taking it?
A: At this time, no one knows. Individuals should discuss any concerns with their personal physicians. The FDA recommends that physicians should evaluate all patients who have received Tysabri for any signs or symptoms suggestive of PML.

Q: Does this suspension mean that Tysabri will never be available to treat MS?
A: Not necessarily. The fate of Tysabri for MS will depend on the results of the investigation of the adverse events that occurred, and a thorough evaluation of the data available from all treated patients involved in the clinical trials of Tysabri. It is possible that Tysabri will be removed permanently from the market, and it is also possible that Tysabri will be returned to the market. That decision is now in the hands of the U.S. Food and Drug Administration.

Q: Is the suspension of Tysabri a setback to the search for a cure?
A: This is certainly a disappointment, but there are many other approaches being taken to treat MS. In the meantime, scientists continue their work to find a cure for this disease.

Q: What should physicians do who have been treating their patients with Tysabri?
A: The FDA recommends that physicians should evaluate all patients who have received Tysabri for any signs or symptoms suggestive of PML. Any suspected cases of PML should be reported to Biogen Idec or the FDA MedWatch Program (1-800-FDA-1088).
Q: What is the risk of developing PML for those individuals who participated in the clinical trials of Tysabri or were prescribed it by their personal physician?
A: The risk at this time remains unknown. Each person in the clinical trials who was given Tysabri is being carefully evaluated for any signs or symptoms of PML. Any person who has been prescribed the medication should stay in contact with his or her physician and report any unusual symptoms, such as motor weakness on one side of the body, rapidly developing changes in mental function, language disturbance, visual disturbance, or change in behavior or personality. It is important to keep in mind that only three confirmed cases of PML have occurred thus far in the more than 8000 individuals who have taken the medication.

Q: Is it possible that the three people who developed PML had the disease in their systems before taking Tysabri?
A: PML is a very rare disease that occurs in patients whose immune systems have been suppressed, most commonly by some forms of cancer, by medications to prevent rejection following organ transplantation, or by AIDS. It is virtually impossible that any of the participants in the clinical trials of Tysabri had PML prior to the trial.

Q: What is the relationship between Tysabri, the JC virus, and PML?
A: At this time, the relationship between Tysabri and PML remains unknown. PML is thought to be caused by the JC virus -- a common virus that lies dormant in most healthy individuals. Biogen Idec convened a panel of physicians and scientists with expertise in PML to try to determine why the JC virus became active in the three individuals diagnosed with PML. This will help determine what, if any, relationship exists between Tysabri and PML. That panel’s findings have now been reported to the FDA.

Q: Two people, out of more than 500 people in the SENTINEL trial who received a combination of Tysabri and Avonex for more than two years, developed PML. What is the risk for the other participants in that trial who took the two drugs for such a long period of time?
A: Unfortunately, doctors are not able to provide immediate reassurance to people who have been on the combination treatment for an extended period of time. Participants in the trial were notified about whether they received Tysabri or placebo with the Avonex, and most participants who were on active Tysabri treatment have been evaluated closely with a repeat MRI and a thorough clinical examination. As of August 9, 2005, no new cases of PML have been uncovered in persons who have taken Tysabri for MS.
Q: How long will those individuals who took Tysabri have to wait in order to know whether or not they will develop PML?
A: Unfortunately, there is currently no precise answer to this question. PML is generally a rapidly progressive disease. This means that any individual who already has unrecognized/undiagnosed PML is likely to develop symptoms in a matter of weeks. Since all patients have now stopped taking Tysabri, the JC virus is presumably less likely to become activated in their systems and therefore unlikely to cause PML in the future. However, this remains a question that cannot be fully answered.

Q: Should those people in the clinical trial who were taking Tysabri and Avonex continue with their Avonex?
A: This is a question that each person will need to discuss with his or her physician.

-- Research & Clinical Programs

*The National MS Society is proud to be a source of information about MS. Our comments are based on professional advice, published experience and expert opinion, but do not represent individual therapeutic recommendation or prescription. For specific information and advice, consult your personal physician.*