

Greetings!

The following is a message from the FDA's Office of Oncology Drug Products Director, Dr. Richard Pazdur:

On August 22, 2008, the U.S. Food and Drug Administration (FDA) approved romiplostim for subcutaneous injection (Nplate™, Amgen Inc.) for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Nplate is a thrombopoietin (TPO) receptor agonist that stimulates bone marrow megakaryocytes to produce platelets. The safety and efficacy of romiplostim were evaluated in two double-blind, placebo-controlled clinical studies of 125 adult patients with chronic ITP who had completed at least one prior therapy and who had baseline platelet counts \leq 30,000/mcL. One study enrolled patients who had undergone splenectomy; the other enrolled patients who had not undergone splenectomy. Patients were randomized (2:1) to romiplostim or placebo. Romiplostim was administered subcutaneously at an initial weekly dose of 1 mcg/kg and subsequently titrated to achieve and maintain platelet counts between 50,000/mcL and 200,000/mcL.

The primary endpoint in both studies was "durable platelet response," defined as at least six weekly platelet counts \geq 50,000/mcL during the last eight weeks of study drug treatment, in the absence of rescue medications during the 24 week treatment period. Romiplostim administration resulted in a durable platelet response in 61% of nonsplenectomized patients and 38% who had undergone splenectomy. Only one placebo group patient achieved a durable platelet response, a patient in the study of nonsplenectomized patients ($p < 0.01$ for the treatment difference in each study). In pooled analyses of the two studies, serious hemorrhage events were reported in 10% of the placebo groups and 6% of the romiplostim groups.

Following completion of the placebo-controlled studies, 100 patients entered an extension study of long term romiplostim therapy. The majority maintained platelet counts \geq 50,000/mcL throughout the study with a median duration of romiplostim treatment of 60 weeks and a maximum duration of 96 weeks. Overall, 271 patients with chronic ITP were exposed to romiplostim. The major safety concerns identified consisted of risks for bone marrow reticulon formation and a risk for worsened thrombocytopenia (compared to baseline) following romiplostim discontinuation. Other potential risks in patients with ITP include marrow fibrosis during long term therapy or thromboses due to excessive platelet increases.

In a single arm trial investigating the use of romiplostim in myelodysplastic syndromes (MDS), 11 of 44 patients were reported as having possible disease progression, among whom four patients developed acute myelogenous leukemia. Randomized, controlled studies will be needed to determine the risks and benefits of romiplostim in these patients. In the controlled studies of patients with chronic ITP, the incidence of hematologic malignancies was low and similar between romiplostim and placebo. Romiplostim is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP. In the controlled studies of patients with chronic ITP, headache was the most commonly reported adverse drug reaction (35% among the romiplostim groups and 32% among the placebo groups).

The major adverse reactions that occurred more frequently in the romiplostim groups

compared to the placebo groups consisted of arthralgia, dizziness, insomnia, myalgia, shoulder pain, abdominal pain and pain in the extremities. Most reactions were of mild to moderate severity. Neutralizing antibody formation to romiplostim was observed in one patient and no patients developed neutralizing antibodies to TPO. The recommended initial dose of romiplostim is 1 mcg/kg once weekly as a subcutaneous injection. Romiplostim must be administered weekly by a healthcare provider. The romiplostim dose is adjusted to achieve platelet counts $\geq 50,000/\text{mL}$ as necessary to reduce the risk for bleeding. Romiplostim should not be used in an attempt to normalize platelet counts. Only prescribers enrolled in the Nplate™ NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) Program may prescribe romiplostim.

Full prescribing information, including details of the NEXUS restricted distribution program, clinical trial information, safety, dosing, drug-drug interactions and contraindications is available at <http://www.fda.gov/cder/foi/label/2008/125268lbl.pdf>

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