

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**BLA 125268**

**OFFICE DIRECTOR MEMO**

July 16, 2008

OFFICE DIRECTOR'S MEMORANDUM

From: Richard Pazdur, MD

Director, Office of Oncology Drug Products

BLA: 125268

DRUG: Romilostim

TRADENAME: Nplate

INDICATION: "for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy

**RECOMMENDED REGULATORY ACTION: APPROVAL**

Refer to Dr. Dwaine Rieves' review serving as the Division Director's Review and the Supplemental Cross Discipline Team Leader Review. This review contains information on the regulatory history of romilostim and a summary of the CMC, nonclinical pharmacology/tox, clinical/statistical reviews. In addition, postmarketing requirements, and REMS are discussed.

**Summary of Key Clinical Trials:**

The safety and efficacy of Nplate 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  $\leq 30,000/\text{mcL}$ . One study enrolled patients who had undergone splenectomy; the other enrolled patients who had not undergone splenectomy. Patients were randomized (2:1) to Nplate or placebo. Nplate 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  $\geq 50,000/\text{mcL}$  during the last eight weeks of study drug treatment, in the absence of rescue medications during the 24 week treatment period. Nplate 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 Nplate groups.

Following completion of the placebo-controlled studies, 100 patients entered an extension study of long term Nplate therapy. The majority maintained platelet counts  $\geq 50,000/\text{mcL}$  throughout the study with a median duration of Nplate treatment of 60 weeks and a maximum duration of 96 weeks.

Overall, 271 patients with chronic ITP were exposed to Nplate. The major safety concerns identified consisted of risks for bone marrow reticulin formation and marrow fibrosis during long term therapy and a risk for worsened thrombocytopenia (compared to baseline) following Nplate discontinuation. Other potential risks include thromboses due to excessive platelet increases and a potential for hematologic malignancy. In the controlled studies of patients with chronic ITP, the incidence of hematologic malignancies was low and similar between Nplate and placebo.

In a single arm trial investigating the use of Nplate in myelodysplastic syndromes (MDS), 11 of 44 patients were reported as having possible disease progression, among whom four patients developed acute myelogenous leukemia. Nplate 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 Nplate groups and 32% among the placebo groups). The major adverse reactions that occurred more frequently in the Nplate groups compared to the placebo groups consisted of arthralgia, dizziness, insomnia, myalgia and various reports of pain throughout the body. Most reactions were of mild to moderate severity. Neutralizing antibody formation to Nplate was observed in one patient and no patients developed neutralizing antibodies to TPO.

The recommended initial dose of Nplate is 1 mcg/kg once weekly as a subcutaneous injection. Nplate must be administered weekly by a healthcare provider. The Nplate dose is adjusted to achieve platelet counts  $\geq 50,000/\text{mcL}$  as necessary to reduce the risk for bleeding. Nplate 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 Nplate (see REMS program below).

This BLA was presented at the March 12, 2008 ODAC meeting and the members unanimously regarded the safety and efficacy data as persuasive of a favorable risk:benefit analysis.

#### **Summary of Post-Marketing Commitments:**

Four post-marketing requirements have been identified. These include of the following:

1. Study 20080009, "A Prospective Phase IV, Open-Label, Multi-Center, Study Evaluating the Changes in Bone Marrow Morphology in Subjects Receiving Romiplostim for the Treatment of Thrombocytopenia associated with Immune (Idiopathic) Thrombocytopenia Purpura (ITP)." At least 150 patients will receive romiplostim and undergo bone marrow evaluations prior to, during and following the completion of romiplostim administration. A similar evaluation schedule will apply to the detection of antibody formation to Romiplostim and thrombopoietin as well as the

electrocardiographic (ECG) detection of cardiac conduction abnormalities. Final report is due by November, 2014.

2. "Antibody Registry Study" that will enroll subjects who have received Romiplostim and whose blood samples contain antibodies to either romiplostim or thrombopoietin. The antibody assays will be performed by Amgen in response to spontaneously submitted requests for the post-marketing blood tests. As described in the romiplostim prescribing information, a lack or loss of response to romiplostim should prompt the healthcare provider to search for causative factors, including neutralizing antibodies to romiplostim. In these situations, healthcare providers are to submit blood samples to Amgen for detection of antibodies to romiplostim and thrombopoietin. The Antibody Registry Study will collect follow-up platelet count and other clinical data sufficient to assess the long term consequences of the detected antibodies. Patients will be followed until the detected antibodies resolve or stabilize in titer over a several month period of time.
3. An observational pregnancy study/registry.
4. A "milk only" lactation study/registry.

#### **Summary of REMS:**

In addition to a medication guide, an FDA has approved a communication plan to include specific text for healthcare provider materials and institutional materials. The education process (as well as prescriber certification/patient registry) is referred to as the "HCP NEXUS" program. Elements to assure safe use includes a drug distribution plan limited to prescribers and patients who enroll in the NEXUS program.

The REMS assessments are to be performed frequently for the first two years following product launch and regularly thereafter. All prescribers must be "certified" by Amgen; certification involves signing a specific document (prescriber enrollment form) that attests to familiarity with the labeling and agreement to comply with the expectations of the NEXUS program/patient registry. The key responsibilities of the prescribers are described below.

- sign and submit the "healthcare provider enrollment form"
- at enrollment of a patient, must complete a "patient enrollment form" and "patient baseline data form."
- obtain signature of each patient to confirm participation in the NEXUS program/disclosure of information to the program
- complete a form every six months to verify that continued treatment is appropriate and to actively solicit (yes/no--check list) major safety outcomes using a "Safety Questionnaire."
- complete a "patient discontinuation" form if Nplate is discontinued; a post-discontinuation form must also be completed six months later (six months after drug discontinuation).

REGULATORY ACTION: I concur with the reviewers of this BLA in approving the above-stated indication.

  
Richard Pazdur, MD  
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