CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125268

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 22, 2008
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Thru:	Claudia Karwoski, Acting Director Division of Risk Management (DRISK) Claudia B. Karwoski 8/22/08
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Subject:	Review of Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Nplate (romiplostim/AMG 531)
Application Type/Number:	BLA 125268
Applicant/sponsor:	Amgen Inc.
OSE RCM #:	2007-2270

CONTENTS

EXECUTIVE SUMMARY

Romiplostim (Nplate) binds to and activates the thrombopoietin receptor and is under review for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenic purpura (ITP) who have an insufficient response to corticosteroids, immunoglobulins, or splenectomy. The Sponsor submitted a proposed risk management program (RMP) with the BLA that inadequately addressed the risks associated with romiplostim. These risks include bone marrow fibrosis, worsened thrombocytopenia after cessation of Nplate thromboembolic complications, an increased risk of hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS), and serious complications due to medication error. OSE's concerns regarding the proposed RMP were addressed in the OSE briefing document for the March 12, 2008 Oncologic Drugs Advisory Committee (ODAC) Meeting. Based on the ODAC discussion and subsequent FDA internal discussions, it was determined that a Risk Evaluation and Mitigation Strategy (REMS) was necessary to ensure that the benefits of romiplostim treatment exceed the risks. The REMS, titled, Nplate NEXUS (Network of EXperts Understanding and Supporting Nplate and patients) Program, submitted on August 12, 2008, includes a Medication Guide, Communication Plan, Elements to Assure Safe Use, an Implementation Plan, and timetable for assessment with the information needed for assessment.

1 BACKGROUND

Romiplostim is a first-in-class fusion "peptibody" that binds to and activates thrombopoietin receptor, inducing the proliferation and maturation of megakaryocytes into platelets. The indication under consideration for approval is for the "treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. Nplate should not be used in an attempt to normalize platelets." The proposed dosing regimen is weight-based (initial dose 1 mcg/kg subcutaneously once weekly). Dosing is titrated weekly to maintain a platelet count $\geq 50 \times 10^9$/L. The maximum dose is 10 mcg/kg. Prior to administration, the lyophilized drug product must be mixed with sterile water for injection. Because of a dosing error observed in the clinical trials, the Sponsor recommends that romiplostim be administered by a healthcare professional.

This mechanism of action makes romiplostim appealing for broad use in a variety of diseases associated with thrombocytopenia. Studies are ongoing for the use of romiplostim to treat thrombocytopenia associated with myelodysplastic syndrome (MDS) and chemotherapy-induced thrombocytopenia (CIT).

The ODAC convened on March 12, 2008 to consider the romiplostim application. The OSE briefing document for the advisory committee meeting is presented in Appendix A. The Committee concluded unanimously that the clinical data demonstrated a favorable risk-benefit profile for certain patients with chronic ITP. Overall, the Committee agreed use should be limited to those with chronic ITP and systematic, regular assessment of all patients for significant clinical reactions was needed. However, they did not support defining any fixed "entry criteria" (i.e., qualifying platelet count), or terms (i.e., intolerant, refractory, or insufficient response to other therapies) to further inform the indication favoring individual physician judgment to recognize the appropriate patient. [1]

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[1] Summary Minutes for the March 12, 2008 Oncologic Drugs Advisory Committee meeting. http://www.fda.gov/ohrms/dockets/ac/cder08.html#OncologicDrugs. Accessed August 20, 2008

1 METHODS AND MATERIALS

1.1 DATA AND INFORMATION SOURCES

The following risk management submissions for Nplate were reviewed:

- Amendment 0018; March 26, 2008
  - FDA comments provided via email on April 8, 2008 and discussed during April 9, 2008 teleconference with Amgen.
- Amendment 0028; April 30, 2008
  - FDA comments provided via email on May 16, 2008 and discussed during May 28, 2008 teleconference with Amgen.
- Amendments 0031 and 0036; June 2 and 24, 2008
  - FDA comments provided via emails to Amgen on June 18, 2008 and June 24, 2008 and discussed during June 25, 2008 teleconference with Amgen.
- Amendments 0037 and 0038; June 27, 2008 (market research plan to assess the effectiveness of Nplate NEXUS Program) and July 8, 2008 (revised physician education, and discontinuation/ post-discontinuation follow-up forms)
  - FDA comments provided via email on July 24, 2008.
- Amendment 0039; August 1, 2008
  - FDA comments provided via email on August 6, 2008.
- Amendment 0040; August 11, 2008
  - FDA comments provided via email on August 11, 2008.
- Amendment 0041; August 12, 2008 and August 21, 2008

1.2 ANALYSIS TECHNIQUES

Each risk management submission was reviewed for responsiveness to FDA comments. The conversion of the risk management plan to a REMS was communicated to the Sponsor in the July 25, 2008, Information Request Letter. The August 1, 11 and 12, 2008 Amgen submissions were reviewed for conformity to the Food and Drug Administration Amendments Act of 2007 (FDAAA) section 505-1 titled, "Risk Evaluation and Mitigation Strategies."

2 RESULTS OF REVIEW

2.1 CONSIDERATION OF REMS

- **The estimated size of the population likely to use the drug involved.**

  The prevalence rate of chronic (adult) immune thrombocytopenic purpura (ITP) ITP was estimated at 24 cases per 100,000 persons or 52,700 adult cases in the United States based on the 2005 census estimates. This prevalence (published in International Society on Thrombosis and Haemostasis by Feudjo-Tepie et al in 2008) was based upon analyses of the Integrated Healthcare Information System (IHCIS) database, one of the largest US health care managed databases. McMillan (Ann Intern Med: 1997) estimates that 30% of chronic ITP cases are "refractory" and this subset is the group of patients who are most

likely to receive romiplostim. Hence, approximately 16,000 patients in the US (based on 2005 census) are general candidates for romiplostim therapy, as indicated.[2]

Romiplostim was granted orphan designation for ITP in March 2003.

- **The seriousness of the disease or condition being treated by the drug.**

  Romiplostim is indicated to treat a very serious stage of chronic ITP that is generally regarded as so serious that patients are at imminent risk of death due to hemorrhage.[2]

- **The expected benefit of the drug with respect to such a disease or condition**

  Two studies of romiplostim for the treatment of chronic ITP were submitted to support the biologic licensing application.[3]

  - Study 1 evaluated patients who had not undergone splenectomy. Patients had been diagnosed with ITP for approximately 2 years and had received a median of three prior ITP treatments. Overall, the median platelet count was 19 x 10^9/L at study entry.
  - Study 2 evaluated patients who had undergone splenectomy. Patients had been diagnosed with ITP for approximately 8 years and had received a median of six prior ITP treatments. Overall, the median platelet count was 14 x 10^9/L at study entry.

  The primary outcome measure was "durable platelet response" defined as achievement of a weekly platelet count $\geq$ 50 x 10^9/L for any 6 of the last 8 weeks of the 24-week treatment period in absence of rescue medication at any time. Sixty-one percent and 38% of patients in Study 1 and 2 respectively, achieved "durable platelet response."[3]

- **The expected actual duration of treatment with the drug.**

  Romiplostim therapy is anticipated as life-long (many years) therapy for many patients. The indication will specifically identify patients with chronic ITP who have had insufficient response to other treatments. This sub-population is one that generally has no other long term therapeutic options and chronic ITP rarely spontaneously resolves.[2]

- **The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.**

  The following risks are outlined in Warning and Precautions section of the romiplostim labeling[3] (in pertinent part):

  - Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis

  Nplate administration increases the risk for development or progression of reticulin fiber deposition within the bone marrow. In clinical studies, Nplate was discontinued

[2] Rieves, D, Division Director Decisional Review Memorandum for the Nplate Risk Evaluation and Mitigation Strategy dated June 16, 2008.

[3] Nplate [package insert]. Thousand Oaks, CA: Amgen; 2008 [DRAFT] submitted on August 12, 2008.

in four of the 271 patients because of bone marrow reticulin deposition. Six additional patients had reticulin observed upon bone marrow biopsy. All 10 patients with bone marrow reticulin deposition had received Nplate doses ≥ 5 mcg/kg and six received doses ≥ 10 mcg/kg. Progression to marrow fibrosis with cytopenias was not reported in the controlled clinical studies. In the extension study, one patient with ITP and hemolytic anemia developed marrow fibrosis with collagen during Nplate therapy. Clinical studies have not excluded a risk of bone marrow fibrosis with cytopenias.

- Worsened Thrombocytopenia After Cessation of Nplate

Discontinuation of Nplate may result in thrombocytopenia of greater severity than was present prior to Nplate therapy. This worsened thrombocytopenia may increase the patient's risk of bleeding, particularly if Nplate is discontinued while the patient is on anticoagulants or antiplatelet agents. In clinical studies of patients with chronic ITP who had Nplate discontinued, four of 57 patients developed thrombocytopenia of greater severity than was present prior to Nplate therapy. This worsened thrombocytopenia resolved within 14 days.

- Thrombotic/Thromboembolic Complications

Thrombotic/thromboembolic complications may result from excessive increases in platelet counts. Excessive doses of Nplate or medication errors that result in excessive Nplate doses may increase platelet counts to a level that produces thrombotic/thromboembolic complications. In controlled clinical studies, the incidence of thrombotic/thromboembolic complications was similar between Nplate and placebo. To minimize the risk for thrombotic/thromboembolic complications, do not use Nplate in an attempt to normalize platelet counts.

- Malignancies and Progression of Malignancies

Nplate stimulation of the TPO receptor on the surface of hematopoietic cells may increase the risk for hematologic malignancies. In controlled clinical studies among patients with chronic ITP, the incidence of hematologic malignancy was low and similar between Nplate and placebo. In a separate single-arm clinical study of 44 patients with myelodysplastic syndrome (MDS), 11 patients were reported as having possible disease progression, among whom four patients had confirmation of acute myelogenous leukemia (AML) during follow-up. Nplate is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.

- **Whether the drug is a new molecular entity.**

  Romiplostim is a new molecular entity and will be the first member of the class of thrombopoietin mimetic agents approved by the FDA.[2]

In summary, romiplostim has shown to be effective for the treatment of thrombocytopenia associated with chronic ITP in patients who have had an insufficient response to other

treatments and it fulfills an unmet need for this specific ITP sub-population. However, there are serious safety concerns that require careful consideration, regular re-evaluation of the benefit risk for each patient, and long-term, periodic follow-up throughout the treatment course with romiplostim. A REMS is required to make certain that the use of romiplostim coincides with periodic re-evaluation and safe use assessment to ensure that the benefit of treatment of chronic ITP with romiplostim exceed the risks of bone marrow reticulin formation and bone marrow fibrosis, worsened thrombocytopenia after cessation of romiplostim, thromboembolic complications, increased risk of hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome, and serious complications due to medication error.

2.2 PROPOSED REMS

2.2.1 Goals

The REMS includes the following goals:

- To promote informed risk-benefit decisions before initiating treatment and while patients are on treatment to ensure appropriate use of Nplate (romiplostim)
- To establish the long-term safety and safe use of Nplate (romiplostim) through periodic monitoring of all patients who receive Nplate (romiplostim) for changes in bone marrow reticulin formation and bone marrow fibrosis, worsened thrombocytopenia after cessation of Nplate, thrombotic/thromboembolic complications, hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS), and medication errors associated with serious

2.2.2 REMS Elements

The REMS includes a Medication Guide, Communication Plan, Elements to Assure Safe Use, an Implementation Plan, and timetable for assessment with the information needed for assessment. These are each described below. The final REMS is presented in Appendix B.

2.2.2.1 Medication Guide

The Medication Guide will be delivered by the Regional Medical Liaisons (RMLs) and sales representatives prior to program enrollment, made available through the Nplate.com website, and included in each Nplate vial package.

A Medication Guide will be dispensed with each Nplate dose. Each healthcare provider will provide each patient with the Nplate Medication Guide prior to each dose. Through the Nplate NEXUS Program, described below, HCPs and patients will confirm they have jointly reviewed the Medication Guide. Patients may be educated by the enrolled prescriber or an HCP under that prescriber's direction.

2.2.2.2 Communication Plan

Amgen will implement a communication plan to healthcare providers to support implementation of the REMS.

Educational materials and the Medication Guide will be distributed to HCPs prior to ordering Nplate. The communication plan consists of the following:

- **Nplate NEXUS Program Website**
  The Nplate NEXUS Program website will be included as a link on the Nplate.com

website. This site will contain information about the Nplate NEXUS Program as well as PDF versions of program forms and tools.

- **Nplate NEXUS Program Healthcare Provider Introductory Letter**
  The Nplate NEXUS Program Healthcare Provider Introductory Letter will be distributed to healthcare providers via the Nplate NEXUS website at product launch along with other Nplate NEXUS Program educational materials. The letter will state that Nplate is only available through the Nplate NEXUS Program. HCPs must be enrolled in the program to prescribe Nplate and patients must be enrolled in the program to receive Nplate. Additionally, the letter will provide a description of the program created to establish the long-term safety and safe use of Nplate and the prescribers' role. Finally, the letter will include direction on how to enroll in the Nplate NEXUS Program.

2.2.2.3 Elements to Assure Safe Use

The Nplate REMS includes the following elements to assure safe use:

A. Nplate will only be prescribed by healthcare providers who are specially certified under 505-1(f)(3)(A)

Certification of prescribers into the Nplate NEXUS Program requires prescribers to enroll in the Nplate NEXUS Program and attest to safe use conditions. The following materials support the certification process:

- Nplate NEXUS Program Healthcare Provider Enrollment Form
- Nplate NEXUS Program Brochure
- Nplate NEXUS Program Training Kit Folder
- Nplate Dose Calculator
- Nplate NEXUS Program Website
- Nplate NEXUS Program Call Center

B. Nplate will only be dispensed by practitioners and healthcare settings (i.e., hospitals/institutions) that are specially certified under 505-1(f)(3)(B)

In addition to individual HCP enrollment, hospitals/institutions can enroll in the Nplate NEXUS Program. This enables hospitals/institutions to order Nplate through a central pharmacy for inpatient or outpatient dispensing. Each enrolling institution may designate a person to be the point of contact for the institution. The designated person may be a hospital administrator, pharmacy director, clinical pharmacist, or any staff member the institution deems appropriate to internally coordinate the logistics of the program. In addition to the enrollment of a designated person at a hospital, each healthcare provider who prescribes Nplate needs to be enrolled in the Nplate NEXUS Program. Institution enrollment does not circumvent the need for each individual prescriber to be enrolled.

In order to enroll, the designated person will complete an Nplate NEXUS Program Institution Enrollment Form and attest to safe use conditions in the inpatient or outpatient clinic setting along with specific product tracking requirements.

<u>Product Tracking</u>

In order to monitor enrollment and verify that all patients are enrolled in the Nplate NEXUS Program the following audits will be conducted:

- **Order monitoring:** The Nplate™ NEXUS Program verifies that the ordering HCP is enrolled in the program and is treating active patients prior to shipping Nplate

- **Vials shipped monitoring**: An audit system will be in place to compare Nplate shipments to active patients enrolled in the program. For each HCP or Institution, shipment volumes will be compared to expected volumes based on historical purchase patterns and volume expectations based on the number of enrolled patients. Shipment volumes that are outside of expected parameters will be investigated and resolved by contacting the HCP or Institution and reconciling the shipment to patients treated.
- **Patient roster monitoring:** As part of the 6-month safety monitoring, the Nplate NEXUS Program will confirm the roster of actively treated patients. HCP will be presented with the roster of active patients according to Nplate™ NEXUS Program records and requested to confirm their status.

The initial proposed audit criteria is that every four weeks, the number of vials shipped to an HCP or institution is compared to the number of enrolled patients. If more than 2 vials per enrolled patient week are shipped, the HCP or Institution is lagged for follow up. If an HCP or Institution is flagged for any 8 week period, then the Nplate NEXUS Program will contact the HCP or Institution and reconcile the last 4 weeks of shipments. Audit criteria will be assessed on an ongoing basis and amended as appropriate.

On a semiannual basis, Amgen will perform a review of a select sample of institutions to assess their degree of compliance with the program. The sample size will be of at least 5% of the total number of enrolled institutions and consist of randomly selected institutions and/or institutions for which the number of vials shipped over a set period of time does not appear to be consistent with the expected usage based on the number of patients treated at the institution (e.g., more than 8 vials per enrolled hospitalized patients over 4 weeks). The reviewed institutions will be contacted and asked to provide copies of their drug reconciliation and accountability records for the set time period.

The following materials support the HCP/Institution certification and ordering processes:

- Nplate NEXUS Program Healthcare Provider Enrollment Form
- Nplate NEXUS Program Institution Enrollment Form
- Nplate NEXUS Program Brochure
- Nplate NEXUS Program Training Kit Folder
- Nplate Dose Calculator
- Nplate NEXUS Program Website
- Nplate NEXUS Program Call Center
- Procedures for Direct Shipment to Registered Healthcare Providers and Institutions
- Procedures for Monitoring and Compliance of Nplate NEXUS Program Elements

C. Each patient treated with Nplate is enrolled in a program for documentation of safe-use conditions under 505-1(f)(3)(D)

Patients are enrolled into the Nplate NEXUS Program by their prescriber before initiating Nplate treatment. Part of the enrollment requires patients to attest to understanding the risks, reporting adverse events to their prescriber, and understanding that in order to receive Nplate, they will be automatically enrolled in the Nplate NEXUS Program so their healthcare provider can continually evaluate the appropriateness of continuing Nplate and report adverse events to Amgen.

The following materials support the certification process:

- Nplate NEXUS Program Patient Enrollment Form

- What is Nplate NEXUS Program? – a brochure for Nplate patients and caregivers
- Patient ID Card and Dosing Tracker

D. Each patient is subject to certain monitoring under 505-1(f)(3)(E)

Prescribers must complete an Nplate NEXUS Program Patient Baseline Data Form for each patient within 30 days of enrollment and an Nplate NEXUS Program Safety Questionnaire every six months during treatment with Nplate. The Nplate NEXUS Program Safety Questionnaire also requires the prescriber to authorize continued treatment with Nplate. The Safety Questionnaire includes specific questions about the following risks:

- Thrombosis/thromboembolism
- Hematological malignancy
- MDS
- Medication error associated with a serious outcome
- Bone marrow reticulin formation
- Bone marrow fibrosis

The Nplate NEXUS Program Call Center will remind the Nplate prescriber when it is time to complete the questionnaires for each patient. All reported serious adverse events will be further investigated and followed by Amgen Global Safety. In addition, risk-specific follow-up forms were developed to address the above mentioned risks and facilitate more consistent data collection.

An independent External (non-Amgen) Advisory Panel will be established to provide an objective assessment of the predefined SAE data; the Panel will be scheduled to meet semiannually. All serious, medically confirmed AEs will be reported in the Periodic Safety Update Report (PSUR) to FDA.

At the time the prescriber determines that a patient should be discontinued from Nplate, the Nplate NEXUS Program Discontinuation/Post-Discontinuation Follow-up Form must be completed at the time of discontinuation and 6 months later.

The following materials support the monitoring component:

- Baseline Data Form
- Safety Questionnaire
- Risk-Specific Safety Questionnaires (thrombotic complications, hematological malignancy, medication error associated with serious outcomes, bone marrow reticulin/bone marrow fibrosis, worsened thrombocytopenia after cessation of treatment with Nplate)
- Discontinuation/Post-Discontinuation Follow-Up Form
- Nplate Safety Registry document

2.2.2.4 Implementation System

The REMS also includes an Implementation System to monitor and evaluate implementation of some of the elements to assure safe use.

2.2.2.5 Assessment of REMS

The Sponsor will submit a REMS Assessment to FDA every 6 months for the first 24 months following approval, then annually (from REMS approval date) thereafter.

The REMS Assessments will include the following information (more details are provided in Appendix B):

- An assessment of enrollment and discontinuation statistics for patients, prescribers, and institutions
- A narrative summary with analysis of patients who discontinued Nplate treatment including duration of treatment and the reason for discontinuation during the reporting period
- The numbers, summary, and analysis of safety stock orders requested, filled, and denied by prescribers and institutions during the reporting period
- A narrative summary with analysis of reports with inpatient to outpatient (or vice versa) transition issues
- An assessment of use data establishing the circumstances of the use of Nplate
- An assessment of prescriber compliance with requirements of the REMS
- An assessment of institution compliance with requirements of the REMS
- The total, number, percentage of patients, narrative summary, and analysis of the adverse events identified on the Safety Questionnaire and Reauthorization.
    - Where clinical data are incomplete concerning events of interest (e.g., bone marrow fibrosis, hematological malignancy, thrombotic/thromboembolic complications, worsened thrombocytopenia upon cessation of Nplate, serious complications due to medication error, and death) or data points of interest, the report will include a complete description of Amgen's attempts to obtain the missing data. If necessary to establish the cause of death for a patient receiving Nplate, Amgen will obtain information from the National Death Index of the National Center for Health Statistics, Centers for Disease Control.
- A summary and analysis of unintended interruptions in treatment (e.g., interruptions due to shipment delays and other logistical issues). This summary should describe any corrective actions taken.
- A summary of all the changes to the Nplate NEXUS Program that were implemented during the reporting period.
- A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- An assessment of healthcare provider and patient understanding regarding the safe-use of Nplate (i.e., the results of surveys administered to prescribers and patients). The survey instrument and methodology will be developed after the product labeling and the educational materials are finalized and will be provided to the FDA for review and comment at least 2 months before it is administered to prescribers and patients in the field. The survey protocol will include the sample size and confidence intervals associated with that sample size; how the sample will be determined (selection criteria); the expected number of physicians to be surveyed; how the participants will be recruited; how and when the surveys will be administered; and an explanation of controls used to minimize bias.

2.3 PROPOSED PHARMACOVIGILANCE PLAN

On May 30, 2008, Amgen agreed to expedited reporting of bone marrow fibrosis, malignancy/malignancy progression, and medication error resulting in a serious adverse event. In

addition, suspected unexpected serious adverse reactions (SUSARs) will be deemed related to Nplate treatment by default and reported to the agency in an expedited manner as 15 day reports.

3 DISCUSSION

The sponsor has proposed a REMS that requires prescriber, institution, and patient enrollment with patient monitoring and documentation of safe use conditions in order to 1) ensure that patients promote informed risk benefit decisions before and during romiplostim treatment and 2) establish the long-term safety and safe use of romiplostim through periodic monitoring.

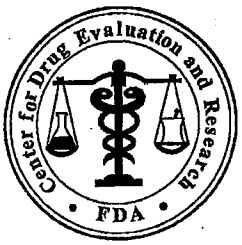
The revised proposal submitted by Amgen on August 12, 2008, adequately responds to the questions posed by OSE and OND to the Advisory Committee during the March 12, 2008 meeting and in subsequent teleconferences with Amgen. This submission is consistent with section 505-1 "Risk Evaluation and Mitigation Strategies" of FDAAA. The romiplostim REMS is comprised of a Medication Guide, Communication Plan, Elements to Assure Safe Use, Implementation Plan, and timetable for assessment with the information needed for assessment.

4 CONCLUSION

The REMS proposal submitted on August 12, 2008 contains components appropriately to include in a REMS. We believe that a REMS comprised of these components will appropriate evaluate and mitigate the risks of bone marrow reticulin formation and bone marrow fibrosis, worsened thrombocytopenia after cessation of romiplostim, thromboembolic complications, increased risk of hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome, and serious complications due to medication error.

APPENDICES

APPENDIX A: OSE BRIEFING DOCUMENT FOR MARCH 12, 2008 ODAC



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 12, 2008
To:	Rafel (Dwaine) Rieves, M.D., Director (Acting) Division of Medical Imaging and Hematology Products (DMIHP)
Thru:	Gerald Dal Pan, M.D., M.H.S., Director Office of Surveillance and Epidemiology (OSE)
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Subject:	Review of risk management proposal and additional considerations
Drug Name(s):	Romiplostim/AMG 531
Application Type/Number:	BLA 125268
Applicant/Sponsor:	Amgen Inc.
OSE RCM #:	2007-2270

EXECUTIVE SUMMARY

Because the clinical trial experience involved relatively small numbers of patients and limited duration of exposure, the extent and significance of the available safety data are inadequate to elucidate fully the significance of certain safety concerns.

If the Advisory Committee concludes that romiplostim provides a meaningful therapeutic benefit and/or fulfills an unmet need for patients in whom the benefit exceed the potential (long term) risks, approval of this product should be contingent upon the Sponsor's commitment to a comprehensive risk management plan with elements to assure safe use and further study of the drug to resolve the stated uncertainties. This would include clear identification of the appropriate population for use and selection of the appropriate tools to (1) communicate the risks, (2) ensure appropriate patient selection, and (3) provide consistent monitoring. In addition, the risk management plan should incorporate an assessment tool to provide for data collection to evaluate fully the effects of romiplostim over time.

1 BACKGROUND

1.1 PRODUCT INFORMATION

Romiplostim is a first-in-class fusion peptibody that binds to and activates thrombopoietin receptor, inducing the proliferation and maturation of megakaryocytes into platelets. This mechanism of action makes romiplostim appealing for broad use in a variety of diseases associated with thrombocytopenia. At present, the Sponsor is proposing romiplostim for the treatment of thrombocytopenia in adult patients with chronic idiopathic (autoimmune) thrombocytopenic purpura (ITP) who are (1) non-splenectomized and have an inadequate response or are intolerant to corticosteroids and/or immunoglobulins or (2) are splenectomized and have an insufficient response to splenectomy. Studies are ongoing for the use of romiplostim to treat thrombocytopenia associated with myelodysplastic syndrome (MDS) and chemotherapy-induced thrombocytopenia (CIT).

For the treatment of ITP, the Sponsor studied a weight-based dosing regimen (initial dose 1 mcg/kg subcutaneously once weekly). Dosing is titrated weekly to maintain a platelet count $\geq 50x10^9$/L. The maximum dose is 10 mcg/kg. Prior to administration, the lyophilized drug product must be mixed with sterile water for injection. Because of a dosing error in the clinical trials, the Sponsor recommends that romiplostim be administered by a healthcare professional.

1.2 SAFETY CONCERNS

While the efficacy appears robust based on the outcomes of two placebo-controlled, blinded clinical studies, the drug product has certain risks that are not yet completely characterized. There is biologic plausibility that romiplostim has the potential to induce unexpected cell proliferation, platelet activation and/or thrombosis. Based on these theoretical concerns and the adverse events noted in clinical trials, the following risks were identified for further risk management consideration:

- **Neoplasm progression**: Thrombopoietin receptors are expressed on the surface of myeloid cells. There is no confirmed expression on solid tumors.[4] Patients with any known history of marrow stem cell disorder or any "active" (no "active" cancer in past 5

[4] Risk management plan. Amgen; dated September 14, 2007. p.78.

years) cancer were excluded from the ITP studies.[5] The Agency noted development of acute myelogenous leukemia or chloroma in patients with MDS treated with romiplostim in phase 1 and 2 clinical trials for treatment of thrombocytopenia associated with MDS. Questions arise regarding how to screen patients effectively and what is the risk of malignancy progression with long term romiplostim exposure in ITP patients with a history of malignancy.

- **Reticulin formation/marrow fibrosis**: There is concern that with prolonged exposure to romiplostim, increased reticulin will lead to adverse clinical sequelae (e.g., myelofibrosis, collagen fibrosis, chronic idiopathic myelofibrosis, or bone marrow fibrosis with cytopenia). Overall, increased reticulin was reported in six subjects exposed to romiplostim in the ITP safety database.[6] All patients had undergone splenectomy and all had nucleated red blood cells on peripheral smear. None had bone marrow consistent with myelofibrosis. The doses used were high, ranging from 7 to 15 mcg/kg/dose.[6] Based on the observed cases, the medical officer states that increased reticulin appears to be a dose-dependent adverse effect.[6] All cases were in patients with highly refractory disease which coincides with the possible need for dose escalation. The Sponsor states that this safety concern has been detected through routine monitoring of peripheral blood smear and a decline in platelet count response. However, the Sponsor also states that no well-characterized biomarkers are available that could help predict the incidence of reticulin in ITP subjects. Bone marrow biopsy is the only reliable way to determine the presence of reticulin. Biopsy is not consistent with routine management of ITP patients.[7] Questions arise regarding the significance of the event, the long-term sequelae, how best to monitor this finding, and if/how best to treat this finding/event (lower dose, discontinue romiplostim, watchful waiting). If romiplostim discontinuation is warranted, the risk of possibly significant rebound thrombocytopenia must be considered.

- **Thrombotic events**: Thrombotic complications are a concern particularly when platelet counts exceed the normal range. The Sponsor lists it as theoretical concern and states that adverse event rates were similar between placebo and romiplostim. Difficulty with delivering a consistent dose along with the inability to make small dosage adjustments are contributing factors to this risk. Typical dose volumes range between 0.1 to 0.2 mL. Therefore, small volume changes can result in significant dose alterations. The degree of platelet count fluctuation observed in the clinical studies may have resulted, in part, from the difficulties of being able to deliver an accurate dose, consistently. Further, these fluctuations required the Sponsor to broaden the target platelet range from $50\text{-}100 \times 10^9$/L to $50\text{-}200 \times 10^9$/L in the absence of any justification for benefit for higher platelet counts in ITP patients.[6] The ability to modify precisely a patient's dose or deliver the same dose consistently could avoid such medication errors that may result from continually adjusting a patient's dose in reaction to fluctuations, exposing patients to higher doses than necessary and increasing the risk of experiencing an adverse event. The importance of proper dose preparation and administration and close platelet count monitoring need to be addressed.

- **Immunogenicity**: During clinical trials, antibody formation to romiplostim and endogenous thrombopoietin were noted. At least one case of neutralizing antibodies was also identified. Based on information provided at the time of submission, antibody

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[5] Risk management plan. Amgen; dated September 14, 2007. p. 32.

[6] Lee J. Interim clinical review for romiplostim in ITP. January 16, 2008.

[7] Background information for ODAC meeting, March 12, 2008. Amgen; submitted on February 8, 2008.

formation did not affect the effectiveness of romiplostim. However, the sustained efficacy over the long term has not been fully assessed. Therefore, monitoring platelet counts, dose escalation, and creating a clear plan for antibody formation detection may be prudent.

- **Recurrence of thrombocytopenia after cessation of treatment**: Recurrence of thrombocytopenia, markedly below baseline, was reported in phase 1 and 2 dose-finding studies upon drug discontinuation. There were no reports of these events in phase 3 studies because patients were transitioned to the open-label extension study. Thrombocytopenia may be exacerbated by anticoagulant/anti-platelet therapy. It will be important to highlight this phenomenon to prescribers.

2 RISK MANAGEMENT OF ROMIPLOSTIM

Risk management encompasses risk minimization strategies as well as risk assessment strategies.[8] Both of these components are equally necessary in order to develop a sufficient program to minimize the known and potential risks and assess the potential effects of romiplostim in the long term.

Risk Minimization

The romiplostim RiskMAP should minimize risk by (1) ensuring appropriate patient selection; (2) educating prescribers about the appropriate patient selection, drug dosing, preparation, and administration technique and use the lowest effective dose to maintain a platelet count at the minimum concentration necessary to avoid negative sequelae; and (3) educating patients about the risks so that he or she can make an informed decision to proceed or to refuse treatment with romiplostim.

Various tools/strategies work to minimize risks associated with drugs and therapeutic biologics. Tools communicate specific risk information as well as information regarding optimal product use. Tools provide guidance and/or assure adherence to certain prescribing/dispensing requirements, and/or limit use of a product to only the most appropriate situations or patient populations.

Risk Assessment

The romiplostim RiskMAP should assess the risk of the following in all treated patients:

- Neoplasm progression (however this may be difficult if patients with a history of neoplasm are excluded)
- Reticulin formation
- Thrombotic complications
- Antibody formation contributing to reduced efficacy through dose escalation and antibody testing
- Clinically important sequelae upon romiplostim discontinuation

2.1 SUMMARY OF SPONOSOR'S PROPOSED RISK MANAGEMENT PLAN[7]

The RiskMAP submitted to the Agency on February 7, 2008, was reviewed. The program "is designed to ensure appropriate use of romiplostim in ITP patients, minimize use of romiplostim in patients with thrombocytopenia caused by a condition other than ITP, and promote informed

[8] Guidance for Industry: *Development and Use of Risk Minimization Action Plans.* Finalized March 2005.

risk-benefit decision regarding romiplostim use."[9] The Sponsor proposes to meet these goals through labeling, targeted education and outreach, routine pharmacovigilance and four studies to assess risk.

Proposed Labeling

The proposed Warnings and Precautions section of the label will include information regarding the risk of malignancies and progression of malignancies, recurrence of thrombocytopenia after treatment discontinuation, increased reticulin formation, thrombotic/thromboembolic complications, and antibody formation. The Dosage and Administration section provides additional information on calculating and preparing the dose of romiplostim. In addition, the label states that romiplostim "must be administered by a healthcare professional." The Sponsor does not explain how this will be ensured.

Targeted Education and Outreach

The Sponsor submitted a Medication Guide for patients. It is unclear who will be responsible for distributing the Medication Guide to the patient. Since a healthcare practitioner must administer the dose on a weekly basis, the Sponsor may utilize alternative drug distribution plans which may deviate from typical drug distribution (manufacturer → wholesaler → pharmacy → patient).

In order to "minimize the risk of physician inadvertently treating an MDS or hematopoietic malignancy patient with romiplostim, Amgen created a rigorous risk communications platform that is supported by three interconnected components."[10] Briefly, these components consist of targeting only qualified specialists for training, a "pre-use checklist along with each product purchase," and a "training kit." The "training kit" provided to prescribers will include patient-directed disease state information. None of the materials were provided in Amgen's background document.

Amgen proposes a variety of routine educational efforts directed at healthcare professionals such as continuing education programs, face-to-face education (detailing), and dissemination of safety information through sales force. In absence of the actual materials, it is difficult to determine if these efforts will truly serve an educational purpose or function primarily to promote and market romiplostim.

Pharmacovigilance

The Sponsor proposes the following measures:

- Post-marketing safety surveillance for the required periodic safety update reporting
- Advisory panels/safety monitoring committee involvement in on-going and future clinical studies
- An adverse event questionnaire: This questionnaire will be used to document reticulin and progression of myeloid malignancy events reported through clinical trials and the Sponsor's spontaneous reporting system.

Risk Assessment

The Sponsor proposes the following studies:

- Retrospective observational study (Protocol 20070796) to define the background prevalence of bone marrow reticulin who have not received romiplostim: This study will

[9] Background information for ODAC meeting, March 12, 2008. Amgen; submitted on February 8, 2008. p.79.

[10] Background information for ODAC meeting, March 12, 2008. Amgen; submitted on February 8, 2008. p. 90.

assess the prevalence and nature of bone marrow reticulin and bone marrow fibrosis in adults with chronic ITP in Denmark. It will also evaluate the incidence of thrombotic events. Historical data on 1,500 patients with ITP will be collected from 1996 to 2007 using the National Health Registry Databases of Denmark.

- Registry to monitor the incidence of increased bone marrow reticulin and potential risk of bone marrow fibrosis (Protocol 20070797): This cohort study will include all adult patients identified as having chronic ITP in Denmark, Sweden, and Finland, between January 1, 2009, and December 31, 2019 from hospitalized and outpatient records regardless of romiplostim exposure. Study subjects would be followed from one to ten years. Cases with bone marrow abnormalities would be ascertained using electronic medical records. Of note, romiplostim is not approved in these countries.[11]
- Long term prospective study to assess changes in bone marrow morphology: This study will include 200 patients with ITP receiving romiplostim to capture long-term bone marrow changes. Bone marrow biopsy, peripheral blood smear, and sampling for antibody testing will be completed at baseline before romiplostim exposure as well as after 24 months and 60 months of romiplostim exposure. The primary endpoint will be the incidence of increased reticulin at month 24 and month 60 over baseline.
- Romiplostim utilization study: This study will use data form the PharMetrics Patient Centric Database, HealthCore Managed Care Database, and the national health registry systems of Denmark, Sweden, and Finland. Assessment will be conducted at 9, 15, and 27 months after launch. This study will attempt to:
    - estimate the proportion of patients treated with romiplostim for off-label indications,
    - estimate the proportion receiving more than the maximum labeled dose,
    - describe romiplostim treatment and utilization patterns (up to 39 months) among chronic ITP patients, and
    - compare treatment and utilization patterns among chronic TIP patients who are and are not treated with romiplostim.

Additional Measures

In addition to the strategies outlined above, the Sponsor states that no direct-to-consumer media advertising will be used.

Program Evaluation Plan

The Sponsor plans to report semiannually on the overall program with an option to reduce or expand use of particular tools based on the following:

- assessment of comprehension, knowledge, attitude, and desired safety behaviors about drug safety risks in healthcare providers as a result of the educational efforts (prescriber, pharmacist, nurse)
- evaluation of the effectiveness of the Medication Guide delivery through surveys (web-based) and other tools
- market research on platelet counts at the time of treatment initiation and values achieved during treatment, duration of therapy, doses used, monitoring of off/on-label use
- surveys of patients and patient advocacy groups on knowledge regarding ITP and romiplostim

[11] Risk management plan. Amgen; dated September 14, 2007. p. 80. Internal communication with the Division of Medical Imaging and Hematology Products (DMIHP) on February 11, 2008.

2.1.1 COMMENTS ON SPONSOR PROPOSAL

The Sponsor proposes an education-based RiskMAP that focuses on appropriate patient selection and further risk assessment. While we agree with the risk assessment and minimization goals, certain components of the plan are missing that if included, would better ensure safe use and adequate risk assessment. Considering the biologic plausibility for significant adverse events coupled with the limited number patients exposed[12] over a relatively short period of time in the clinical development program[13] and the anticipated broader use in a traditional post-approval environment, these concerns build a case for implementation of additional risk mitigation strategies.

The proposal fails to identify the appropriate use population. Neither the RiskMAP nor the proposed label clearly outlines who should or should not receive romiplostim based on the risk/benefit profile. For example, the label does not state whether prescribers should expose ITP patients with a history of bone marrow disorder or "active" cancer to romiplostim.

The RiskMAP fails to describe how appropriate use will be ensured. Instead, it focuses on education-based initiatives designed to encourage appropriate use. These educational tools are important to communicate the message(s), but there is limited experience on their effectiveness in ensuring safe use of a product. Traditional risk communication tools such as labeling and dear healthcare professional letters have been shown to have little effect on impacting prescribing behavior or increasing compliance with labeled laboratory monitoring recommendations.[14,15,16,17]

- One focus of the proposal is the strategy to target only qualified specialists (hematology, medical oncology, hematology-oncology) to enhance appropriate use. This plan may be ineffective given that hematologists/oncologists are expected to comprise the vast majority of use, on and off-label. With only a proposed ITP indication at this time, the need to target oncologists is difficult to justify and may serve to encourage rather than discourage off-label use (e.g., use in CIT). Therefore, the impact of this initiative on minimizing off-label use is possibly unfavorable to inconsequential, at best.
- The Sponsor also proposes a checklist (not provided) with each product purchase. It is not clear if a checklist(s) will be provided with each vial or each shipment. It is not clear how the checklist will be implemented or what leverage this effort will ultimately have on appropriate patient selection in the absence of measures to ensure its appropriate use. How the checklist will be implemented will depend in part upon who purchases and receives the product. Since romiplostim is to be administered by healthcare professionals only, it is unclear if romiplostim will be sold directly to prescribers for administration or if retail pharmacies will order this product to dispense to the patient to take to a healthcare professional for administration. If the latter, it is unclear how the checklist

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[12] The ITP safety set consists of only 204 patients (284 total including all studies) who were exposed to at least one dose of romiplostim. Data from the risk management plan submitted by Amgen dated September 14, 2008. p.23.

[13] Only 74 patients had at least 52 weeks of exposure. Data from the background information for ODAC meeting, March 12, 2008. Amgen; submitted on February 8, 2008. p. 62.

[14] Willy M, et al. *A study of compliance with FDA recommendations for pemoline (Cylert)*. J Am Acad Child Adolesc Psychiatry. 2002 Jul;41(7):785-90.

[15] Graham D, et al. *Liver enzyme monitoring in patients treated with troglitazone*. JAMA. 2001 Aug 15;286(7):831-3.

[16] Smalley W, Shatin D, Wysowski D, Gurwitz J, Andrade S, et al. *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action*. JAMA 2000;284(23):3036-3039.

[17] Weatherby LB, Nordstrom BL, Fife D, Walker AM. *The Impact Of Wording in "Dear Doctor" Letters and In Black Box Labels*. Clin Pharmacol Ther. 2002;72:735-742.

will be of any value to the prescribing physician in selecting the appropriate patient when the decision to treat the patient has been made and the prescription has been written and dispensed.

Four studies are proposed to assess bone marrow reticulin risks, potential thromboembolic events, and patterns of prescribing. These studies are unlikely to adequately characterize and manage the identified and potential risks associated with romiplostim. Two of the four proposed studies will be completed in non-U.S. populations.

The Retrospective Observational Study (Protocol 20070796) proposes to evaluate the background prevalence and incidence of bone marrow reticulin and thrombotic events in non-US ITP populations. This study would provide information on background rates regardless of romiplostim approval since the study would evaluate incidence/prevalence in ITP patients through 2007. The Sponsor should consider evaluating the prevalence and incidence of bone marrow reticulin and thrombotic events in U.S. ITP populations also using population-based large claims databases with access to medical records. ITP patients can be reliably identified in administration data.[18]

The prospective registry proposes to follow all ITP patients identified from hospital and outpatient records over a ten-year period. The study, however, is limited to Danish, Swedish, and Finnish patients where romiplostim is not yet approved.[11] In concept, this registry would have the potential to provide clinically significant information on bone marrow abnormalities but would be limited to clinical information captured by medical records. This registry, however, may or may not provide information on whether any potential increased risk for bone marrow reticulin abnormalities and neoplasms can be related to the disease progression itself or to romiplostim exposure. There are no estimates of the number of exposed and non-exposed ITP patients and it remains unknown if and when romiplostim will be approved in Denmark, Sweden, and Finland, all non-US populations.

Although the Sponsor describes the third study as a "long term prospective study," this appears to be an open-label follow-up of study subjects treated with romiplostim. This study would be limited to assessing bone marrow morphology in 200 study subjects. Continuous monitoring would include monthly assessments of peripheral blood smears for morphological abnormalities, sampling for antibody testing at baseline as well as after 24 months and 60 months of romiplostim exposure, bone marrow biopsy with reticulin and trichrome staining at screening/baseline and after 24 months and 60 months of romiplostim exposure. The primary endpoint of the trial would be the incidence of increased reticulin at month 24 and month 60 over baseline. This study would characterize the morphology of romiplostim-exposed patients. There is no mention of a comparator group. Also, no information is provided on the nationality of study subjects.

The fourth study proposes to evaluate patterns of romiplostim use using the PharMetrics Patient-Centric Database, HealthCore Managed Care Database, as well as data from the national health registry systems of Denmark, Sweden, and Finland. All databases are adequate to evaluate patterns of care and identify off-label use. The PharMetrics and HealthCore are US-based. Records from PharMetrics are de-identified, however, with no possibility of linking with medical records. The HealthCore database and the European registries offer access to electronic medical records and could be suitable to assess possible risks.

These studies do not provide immediate resolution to the concerns surrounding the risks associated with romiplostim now and cannot ensure safe use for patients who may receive

[18] Segal BM, Powe NR. Accuracy of identification of patients with immune thrombocytopenic purpura through administrative records: A data validation study. Amer J of Hematology.2003;75(1): 12-17.

romiplostim if the product is approved during the current review cycle. Therefore, a restricted distribution risk minimization action plan designed to assure safe use through appropriate patient selection and risk assessment should be considered in conjunction with risk assessments.

2.2 ADDITIONAL RISK MANAGEMENT STRATEGY CONSIDERATIONS

2.2.1 RISK COMMUNICATION

Communication strategies work to inform healthcare professional and patients about conditions of use contributing to produce risk and conditions of use that are important to achieve the products benefits. Dear healthcare professional letters, Medication Guides, informed consent forms (patient agreement forms), and training programs are all examples of different tools. The informed consent process facilitates communication between the patient and prescriber. The result of this communication is the patient's authorization or agreement to undergo treatment with the romiplostim. This process gives the patient the opportunity to ask questions to elicit a better understanding of the treatment, so that the patient can make an informed decision to proceed or to refuse treatment. The purpose is not to obtain agreement to participate in the RiskMAP. Agreement to share/disclose health information is a separate issue. Informed consent is utilized for several products with RiskMAPs including Lotronex, Accutane, Tysabri, Soriatane, and Thalomid.

2.2.2 ENSURING APPROPRIATE USE

Patient Selection

The goal of risk minimization is to minimize a product's risks while preserving its benefits. The first step is to identify a patient population for whom this product has a favorable benefit risk profile and restrict its use to those patients until the risks and long term effects are understood and the need for such measures may no longer be needed. If such a patient population can be identified, the RiskMAP should address how prescribers will identify the patients for whom a favorable benefit/risk profile exists, what risk minimization measures are needed for these patients to safely use the product, and what measures are needed to prevent use in patients for whom the benefit risk profile is not favorable.

Patient Monitoring and Data Collection

Specific goals and objectives are part of the development of a RiskMAP. The goals are translated into measurable program objectives that lead to achievement of the RiskMAP goals. These objectives often involve monitoring laboratory tests, imaging, and other examination findings.

Data collection should be comprehensive, and involve all patients prescribed romiplostim since the proposed patient population is limited and closely monitored. Data collection should include, but not be limited to, detection of neoplasm development and/or progression, reticulin formation and subsequent sequelae or absence thereof, thrombotic events, determination of the risk of immunogenicity, and characterization of the risk of thrombocytopenia upon treatment discontinuation. The merits of the proposed risk assessment studies versus data collection through the risk management plan will need further consideration and discussion.

2.3 ELEMENTS OF A POSSIBLE RISKMAP

The considerations described above to minimize exposure and assess long term risk with centralized sources for data collection can be accomplished through a restricted distribution program in which certain conditions for safe use must be met before the product can be

distributed, prescribed, dispensed, and/or administered. These elements are in addition to the communication tools discussed above and might include the following:

a. Mandatory enrollment of prescribers with one or more of the following elements:
    i. Attestation of understanding the safe use condition(s) (e.g., appropriate patient selection, patient counseling and monitoring)
    ii. Agreement to comply with program monitoring and data collection

b. Required registration for distributors/pharmacies

    The Sponsor has not explained how the drug will be distributed. Requirements for the stakeholders involved in distribution will be dependent on how the Sponsor plans to distribute romiplostim.

c. Mandatory enrollment of patients:
    i. Patients sign informed consent
    ii. Comply with monitoring

d. Long-term data collection to assess the following:
    i. Risk of neoplasm progression
    ii. Risk of reticulin formation
    iii. Risk of thrombotic events
    iv. Risk of antibody formation/reduced efficacy
    v. Clinically important sequelae upon romiplostim discontinuation

3 DISCUSSION

The Sponsor's proposal for education, targeted detailing and a checklist may not be sufficient to minimize the risk and ensure appropriate use of the product. The Advisory Committee should discuss the utility of a restricted distribution program for romiplostim. There are a number of characteristics about the drug product and the nature of the disease that make a restricted distribution program feasible. The target patient population is limited and closely monitored. That patient-provider relationship is targeted to a single but significant medical problem that requires chronic, long-term treatment. We anticipate prescribing to be limited to one specialty, primarily hematology – even when potential off-label use is considered. The product's formulation (requires reconstitution, single-use vial vs. fixed dose, prefilled syringe) may limit use. In addition, the Sponsor plans to require administration by a healthcare provider.

There is a unique challenge with developing an adequate RiskMAP for romiplostim. There is not a single identifiable, preventable risk; rather there are several risks that require consideration and long term follow-up. For example, the significance of reticulin formation is not known nor is there an ideal method for detection/monitoring. In the case of malignancy progression, the RiskMAP can mitigate this risk by preventing exposure in patients at risk. However, there are no mitigation options that go beyond gatekeeping and monitoring. Further, the absence of neoplasm cases will not translate to lack of risk. The lack of malignancy cases could demonstrate the effectiveness of the RiskMAP but not provide further insight into malignancy progression. Additional data outside of the RiskMAP would be necessary to evaluate the significance of this risk.

By developing a RiskMAP in which prescribers and patients enroll provides the opportunity to create centralized data collection tools and to ensure appropriate monitoring is performed. It is

particularly important to ensure safe use while risk assessment is ongoing. The Sponsor could choose to prompt the prescriber and monitor for neoplasm progression, reticulin formation/sequelae, and/or antibody formation at regular intervals. A special registry/protocol could be developed for patients for long-term follow-up, if necessary. While the additional studies proposed by the Sponsor could provide additional information, those studies should not be a substitute for or alleviate the need to ensure safe use through careful patient selection, observation and follow-up at the present time. The merits of the proposed risk assessment studies and the merits of data collection through the risk management plan will need further consideration and discussion.

4 CONCLUSION

If the Advisory Committee determines that romiplostim provides a meaningful therapeutic benefit and/or fulfills and unmet need for patients where the benefit exceeds the unknown long term risks, approval of this product should be contingent upon the Sponsor's commitment to a comprehensive risk management plan to assure safe use and to further study of the drug to resolve the stated uncertainties.

APPENDIX B: NPLATE REMS

BLA 125268 Nplate (romiplostim)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

- To promote informed risk-benefit decisions before initiating treatment and while patients are on treatment to ensure appropriate use of Nplate (romiplostim)
- To establish the long-term safety and safe use of Nplate (romiplostim) through periodic monitoring of all patients who receive Nplate (romiplostim) for changes in bone marrow reticulin formation and bone marrow fibrosis, worsened thrombocytopenia after cessation of Nplate, thrombotic/thromboembolic complications, hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS), and medication errors associated with serious outcomes.

II. REMS ELEMENTS

A. Medication Guide

The Medication Guide will be delivered by the Regional Medical Liaisons (RMLs) and sales representatives prior to program enrollment, made available through the Nplate.com website, and included in each Nplate vial package. A Medication Guide will be dispensed with each Nplate dose. Each healthcare provider will provide each patient with the Nplate Medication Guide prior to each dose.

B. Communication Plan

Amgen will implement a communication plan to healthcare providers to support implementation of the REMS.

Educational materials and the Medication Guide will be distributed to HCPs prior to ordering Nplate.

Nplate NEXUS Program Website

- The Nplate NEXUS Program website will be included as a link on the Nplate.com website. This site will contain information about the Nplate NEXUS Program as well as PDF versions of program forms and tools. The tabbed components on the Nplate NEXUS Program website will reflect the REMS goals and the primary content of the Nplate NEXUS Program Brochure. Additionally, all program forms will be available under the resource tab.

Healthcare Provider Awareness

- **Nplate NEXUS Program Healthcare Provider Introductory Letter**
  The Nplate NEXUS Program Healthcare Provider Introductory Letter will be distributed to healthcare providers via the Nplate NEXUS website at product launch along with other Nplate NEXUS Program educational materials. The letter will state that Nplate is only

available through the Nplate NEXUS Program. HCPs must be enrolled in the program to prescribe Nplate and patients must be enrolled in the program to receive Nplate. Additionally, the letter will provide a description of the program created to establish the long-term safety and safe use of Nplate and the prescribers' role. Finally, the letter will include direction on how to enroll in the Nplate NEXUS Program.

C. Elements to Assure Safe Use

1. Nplate will only be prescribed by healthcare providers who are specially certified under 505-1(f)(3)(A)

Certification of prescribers into the Nplate NEXUS Program requires prescribers to enroll in the Nplate NEXUS Program and attest to the following:

- I have read the full prescribing information for Nplate
- I understand that Nplate is only approved 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.
- I understand that Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding.
- I understand that Nplate should not be used in an attempt to normalize platelet counts.
- I understand that Nplate is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.
- I understand the following risks are associated with Nplate:
    - Nplate administration increases the risk for development or progression of reticulin fiber deposition within the bone marrow. Clinical studies have not excluded a risk of progression to bone marrow fibrosis with cytopenias. If the patient develops new or worsening morphological abnormalities or cytopenia(s), I should discontinue treatment with Nplate and consider a bone marrow biopsy, including staining for fibrosis.
    - Discontinuation of Nplate may result in thrombocytopenia of greater severity than was present prior to Nplate therapy. This worsened thrombocytopenia resolved within 14 days in the clinical trials.
    - Thrombotic/thromboembolic complications may result from excessive increases in platelet counts. Excessive doses of Nplate or medication errors that result in excessive Nplate doses may increase this risk.
    - Nplate may increase the risk for hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS)
- I understand that each patient should be monitored as follows to assure safe use of Nplate:
    - Examine the peripheral smear closely to establish a baseline level of cellular morphologic abnormalities.
    - Monitor CBCs, including platelet counts and peripheral blood smears weekly until a stable Nplate dose has been achieved. Thereafter, CBCs, including platelet counts and peripheral blood smears, should be monitored at least monthly.
    - If Nplate is discontinued, I will obtain weekly CBCs, including platelet counts for at least 2 weeks and consider alternative treatments for worsening thrombocytopenia, according to treatment guidelines.
- I understand how to properly dose and administer Nplate in order to prevent medication errors.

- I understand that I must complete this Nplate NEXUS Program Healthcare Provider Enrollment Form to enroll myself in the Nplate NEXUS Program (I only need to enroll once).
- I will enroll each patient by assisting in the completion of the Nplate NEXUS Program Patient Enrollment Form and completing the Nplate NEXUS Program Patient Baseline Data Form. I will complete the Nplate NEXUS Program Patient Baseline Data Form at the time of enrollment or within 30 days of patient enrollment. I understand that baseline data is only to be used to assess for risk factors for adverse events and to evaluate the long-term safety of Nplate.
- I will provide each patient with the Nplate Medication Guide prior to each dose, and counsel each patient on the risks and benefits of Nplate.
- I will complete the Nplate NEXUS Program Patient Enrollment Form for each patient; (1) obtain patient signature acknowledging receipt of Nplate Medication Guide, (2) obtain patient's signature authorizing disclosure of health information related to the Nplate NEXUS Program, and (3) send the completed Nplate NEXUS Program Patient Enrollment Form to the Nplate NEXUS Program for patient enrollment.
- I will counsel each patient to carry a Patient ID Card and Dosing Tracker that identifies the risks with Nplate and contains the Nplate NEXUS Program access number.
- I will evaluate the safe-use and patient status every 6 months to determine whether the patient should continue Nplate and if so, authorize treatment for another 6 months.
- I will notify the Nplate NEXUS Program when a patient discontinues Nplate by completing the Nplate NEXUS Program Patient Discontinuation/Post- months later.
- I will promptly report to the Nplate NEXUS Program any adverse events occurring in the course of the use of the drug as described in the Nplate NEXUS Program Safety Questionnaire.
- I understand that Amgen will be regularly evaluating compliance with the Nplate NEXUS Program, and that Amgen reserves the right to restrict my ability to enroll future patients or take other appropriate measures at any time if I fail to comply with Nplate NEXUS Program requirements.

I further understand that I have sole responsibility for all medical judgments and treatments, and have sole responsibility to, prior to Nplate administration, counsel each patient on the risks of Nplate, and provide each patient with all necessary warnings concerning Nplate.

The following materials support the HCP certification process:

- Nplate NEXUS Program Healthcare Provider Enrollment Form
- Nplate NEXUS Program Brochure
- Nplate NEXUS Program Training Kit Folder
- Nplate Dose Calculator
- Nplate NEXUS Program Website
- Nplate NEXUS Program Call Center

2. **Nplate will only be dispensed by practitioners and healthcare settings (i.e., hospitals/institutions) that are specially certified under 505-1(f)(3)(B)**

   a. Only certified prescribers (as described above) who are enrolled in the Nplate™ NEXUS Program will be able to dispense and administer Nplate. Nplate will be distributed to enrolled certified prescribers via a drop-ship program through which Amgen maintains direct control over who purchases Nplate. The enrolled

certified prescriber may order Nplate through their usual distributor and the distributor will transmit the order to the Nplate™ NEXUS Program.

b. Only practitioners (physicians' offices) and healthcare settings (i.e., hospitals/institutions) enrolled in the Nplate™ NEXUS Program will be able to dispense and/or administer Nplate. In addition to the enrollment of a designated person at a hospital, each healthcare provider who prescribes Nplate™ needs to be enrolled in the Nplate™ NEXUS Program. Enrollment requires the hospitals institutions to:

- develop a system, order sets, protocols, or other measures to ensure that Nplate is only dispensed to inpatients and outpatients (e.g., in a clinic) after verifying that the prescribing healthcare provider and patient are enrolled in the Nplate NEXUS Program;
- train and provide educational materials to appropriate staff responsible for prescribing, dispensing, and administering Nplate regarding the safe and appropriate use of Nplate, program monitoring requirements (including dispensing a Medication Guide with each dose), program adverse event reporting requirements, and institution documentation requirements;
- develop a system to ensure patients started on Nplate as an inpatient are transitioned to an outpatient healthcare provider that is enrolled (or will be enrolled) in the Nplate NEXUS Program; and
- develop a process and system to track Nplate NEXUS Program compliance and cooperate with periodic audits to assure that Nplate is used in accordance with the program requirements.

Product tracking includes the following information:

- Name and unique identification number of the enrolled prescribing healthcare provider
- Unique identifier (program ID number, name, date of birth, address) of the enrolled patient receiving Nplate
- Date of each Nplate order (including number of vials ordered and vial sizes)
- Number of Nplate vials, vial sizes and date of each dose given to each patient
- Overall inventory for the set period of time including the total number of vials ordered (including vial sizes), dispensed, and in stock.

Nplate will only be distributed to enrolled hospitals/institutions via a drop-ship program through which Amgen maintains direct control over who purchases Nplate. The enrolled institution may order Nplate through their usual distributor; the distributor will transmit the order to the Nplate NEXUS Program.

The Nplate NEXUS Program Institution Enrollment Form can be completed and faxed.

The following materials support the HCP/Institution certification and ordering processes:

- Nplate NEXUS Program Healthcare Provider Enrollment Form
- Nplate NEXUS Program Institution Enrollment Form
- Nplate NEXUS Program Brochure

- Nplate NEXUS Program Training Kit Folder
- Nplate Dose Calculator
- Nplate NEXUS Program Website
- Nplate NEXUS Program Call Center
- Procedures for Direct Shipment to Registered Healthcare Providers and Institutions
- Procedures for Monitoring and Compliance of Nplate NEXUS Program Elements

3. **Each patient treated with Nplate is enrolled in a program for documentation of safe-use conditions under 505-1(f)(3)(D)**

Patient enrollment requires the patient to attest to the following:

- Read and understand the Medication Guide for Nplate that my prescriber has given to me.
- Ask and discuss any questions or concerns about Nplate or my treatment with my health care provider.
- Be aware that Nplate is associated with the following risks:
  - Long-term use of Nplate may cause changes in my bone marrow. These changes may lead to abnormal blood cells or my body making less blood cells.
  - When I stop receiving Nplate, my low blood platelet count (thrombocytopenia) may become worse than before I started receiving Nplate.
  - I have a higher chance of getting a blood clot if my platelet count is too high during treatment with Nplate.
  - Nplate may worsen blood cancers. Nplate is not for use in patients with blood cancer or a precancerous condition called myelodysplastic syndrome (MDS).
- Report any adverse events to my prescriber.
- Understand that I should not discontinue Nplate without talking to my health care provider.
- Understand that, if I receive Nplate in the hospital, that upon discharge, I should immediately follow up with a healthcare provider to determine if continued Nplate treatment is appropriate.
- Understand that I should always carry my Patient ID Card and Dosing Tracker.
- Notify the Nplate NEXUS Program if I switch to a different healthcare provider for Nplate treatment by calling 1-877-NPLATE1 (1-877-675-2831).
- Understand that in order to receive Nplate, I will be automatically enrolled in the Nplate™ NEXUS Program. My healthcare provider will monitor how I am doing on Nplate and report to the Nplate NEXUS Program every 6 months about certain serious side effects, and to make sure Nplate continues to be right for me.
- Understand that if I do not sign this Patient Acknowledgement, I will not be enrolled in the Nplate NEXUS Program and will not be able to receive Nplate.

The Nplate™ NEXUS Program Patient Enrollment Form can be completed and faxed to the Nplate™ NEXUS Program at 1-877-NPLATE0 (1-877-675-2830).

The following materials support the certification process:

- Nplate NEXUS Program Patient Enrollment Form
- What is Nplate NEXUS Program? – a brochure for Nplate patients and caregivers
- Patient ID Card and Dosing Tracker

4. Each patient is subject to certain monitoring under 505-1(f)(3)(E)

a. Safety Monitoring - Prescribers must complete a Nplate™ NEXUS Program Patient Baseline Data Form for each patient within 30 days of enrollment and a Nplate™ NEXUS Program Safety Questionnaire every six months during treatment with Nplate. The Nplate™ NEXUS Program Safety Questionnaire also requires the prescriber to authorize continued treatment with Nplate. The Nplate™ NEXUS Program Call Center will remind the Nplate prescriber when it is time to complete the questionnaires for each patient. All reported serious adverse events will be further investigated and followed by Amgen Global Safety. These forms and questionnaires can be completed and faxed to Nplate™ NEXUS Program at 1-877-NPLATE0 (1-877-675-2830), or completed over the telephone.

b. Patient Discontinuation - At the time the prescriber determines that a patient should be discontinued from Nplate, the Nplate™ NEXUS Program Discontinuation/Post-Discontinuation Follow-up Form must be completed at the time of discontinuation and 6 months later.

The following materials support the monitoring component:

- Baseline Data Form
- Safety Questionnaire
- Discontinuation/Post-Discontinuation Follow-Up Form
- Nplate Safety Registry document

D. Implementation System

The Implementation System includes the following:

- Nplate NEXUS Program Call Center will maintain a database of all enrolled certified healthcare settings and practitioners that dispense and/or administer the drug, and patients who have documentation of safe-use conditions to monitor and evaluate implementation of elements
- Nplate NEXUS Program Call Center will monitor distribution of Nplate to determine whether the drug is only drop-shipped to certified hospitals and prescribers who dispense the drug.
- Nplate NEXUS Program Call Center will monitor certified healthcare settings and practitioners ordering to ensure only enrolled patients are receiving Nplate.
- Nplate NEXUS Program Call Center will monitor healthcare setting and practitioner compliance with the baseline data collection, the periodic safety monitoring and reauthorization, discontinuation procedure, and post-discontinuation follow-up of all patients treated with Nplate. If a healthcare setting or practitioner is found to be noncompliant with the Nplate NEXUS Program, Amgen may prevent the healthcare setting or practitioner from enrolling new patients and require the prescriber to order Nplate directly through the Nplate NEXUS Program.

- Based on monitoring and evaluation of these elements to assure safe-use, Amgen will take reasonable steps to work to improve implementation of these elements.

E. Timetable for Submission of Assessment

REMS Assessments (see III below for content) will be submitted to FDA every 6 months for the first 24 months following approval, then annually (from REMS approval date) thereafter.

III. INFORMATION NEEDED FOR ASSESSMENTS

REMS Assessments will include the following information:

- An assessment of enrollment and discontinuation statistics for patients, prescribers, and institutions
  - The number of patients enrolled in the Nplate™ NEXUS Program (during the reporting period and cumulative).
  - The number of patient person-years for enrolled patients in the Nplate™ NEXUS Program.
  - The number of new patients enrolled during the reporting period.
  - The number of patients who received Nplate who were not enrolled (during the reporting period and cumulative).
  - The number of patients who discontinued Nplate (during the reporting period and cumulative).
  - The number of patients who were lost-to-follow-up (during the reporting period and cumulative).
  - The number of patients who discontinue Nplate and are re-enrolled for another course of Nplate treatment (during the reporting period and cumulative).
  - The number of healthcare providers enrolled in the Nplate™ NEXUS Program (during the reporting period and cumulative).
  - The number of new healthcare providers enrolled in the Nplate™ NEXUS Program during the reporting period.
  - The number of enrolled healthcare providers actively prescribing Nplate during the reporting period.
  - The number of healthcare providers who have ordered/prescribed Nplate who were not enrolled (during the reporting period and cumulative).
  - The number of institutions enrolled in the Nplate™ NEXUS Program (during the reporting period and cumulative).
  - The number of institutions who treated a patient with Nplate during the reporting period.
  - The number of institutions who ordered/prescribed/dispensed Nplate that were not enrolled (during the reporting period and cumulative).
- A narrative summary will be written by Amgen Global Safety with analysis of patients who discontinued Nplate treatment including duration of treatment and the reason for discontinuation during the reporting period.
- The total number of safety stock orders requested, filled, and denied for prescribers during the reporting period.
  - A summary and analysis of safety stock orders per prescriber during the reporting period.
- The total number of safety stock orders requested, filled, and denied for institutions during the reporting period.
  - A summary and analysis of safety stock orders per institution during the reporting period.

- A narrative summary with analysis of reports with inpatient to outpatient (or vice versa) transition issues.
- An assessment of use data establishing the circumstances of the use of Nplate
    - The extent of use in the indicated population
    - The extent of use in patients by various baseline data parameters (e.g., platelet count, spleen status, number of previous therapies, duration of ITP, previous treatment with Nplate, age)
    - The extent of use for treatment of thrombocytopenia associated with chemotherapy or MDS
    - The extent of use for treatment for other reasons
    - The extent of use in inpatients
    - The extent of use in outpatients affiliated with a hospital/institution (e.g., clinics)
    - The extent of use in outpatients not affiliated with a hospital/institution (e.g., doctor's office)
- An assessment of prescriber compliance with elements of certification: completing the Nplate NEXUS Program Patient Baseline Data Form, Nplate NEXUS Program Safety Questionnaire with reauthorization, and the Discontinuation/Post-Discontinuation Follow-Up Form for each patient during the reporting period and cumulative.
- The number of prescribers not complying with certification requirements who must order Nplate directly from the Nplate NEXUS Program (no longer allowed to order through a distributor) during the reporting period and cumulative. Describe the types of noncompliance.
- The number and summary of prescribers who were un-enrolled from the Nplate NEXUS Program during the reporting period and cumulative.
- The number of non-compliant institutions that must order Nplate directly from the Nplate NEXUS Program (no longer allowed to order through a distributor) during the reporting period and cumulative. Describe the types of non-compliance.
- A summary of the institution audits performed during the reporting period. This may include but not be limited to the number of institutions audited, describing the institution compliance with prescriber enrollment, patient enrollment, Baseline Data Form completion, and maintaining Nplate product tracking information. This summary should identify any deviations and the corrective actions taken.
- Amgen Global Safety will write a narrative summary and analysis of the following adverse events reported during the reporting period including:
    - Bone marrow reticulin formation
    - Bone marrow fibrosis
    - Newly diagnosed hematological malignancies or MDS
    - Progression of previously diagnosed hematological malignancies or precancerous conditions (e.g., MDS)
    - Worsening thrombocytopenia upon cessation of Nplate
- The total number and percentage of patients who received a bone marrow biopsy due to a change in the patient's peripheral smear (cumulative).
- The total number and percentage of patients who had a diagnosis of bone marrow fibrosis (cumulative).
- The total number and percentage of patients who had a diagnosis of a new hematological malignancy (cumulative).
- The total number and percentage of patients who had progression of a previously diagnosed hematological malignancy (cumulative).
- The total number and percentage of patients who had worsening thrombocytopenia upon cessation of Nplate (cumulative).

- The total number and percentage of patients who had a thrombotic/thromboembolic event (cumulative).
- The total number and percentage of patients who had a serious outcome as a result of a medication error (cumulative).
- Where clinical data are incomplete concerning events of interest (e.g., bone marrow fibrosis, hematological malignancy, thrombotic/thromboembolic complications, worsened thrombocytopenia upon cessation of Nplate, serious complications due to medication error, and death) or data points of interest, the report will include a complete description of Amgen's attempts to obtain the missing data. If necessary to establish the cause of death for a patient receiving Nplate, Amgen will obtain information from the National Death Index of the National Center for Health Statistics, Centers for Disease Control.
- A summary and analysis of unintended interruptions in treatment (e.g., interruptions due to shipment delays and other logistical issues). This summary should describe any corrective actions taken.
- A summary of all the changes to the Nplate NEXUS Program that were implemented during the reporting period. • A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- An assessment of healthcare provider and patient understanding regarding the safe-use of Nplate (i.e., the results of surveys administered to prescribers and patients). The survey instrument and methodology will be developed after the product labeling and the educational materials are finalized and will be provided to the FDA for review and comment at least 2 months before it is administered to prescribers and patients in the field. The survey protocol will include the sample size and confidence intervals associated with that sample size; how the sample will be determined (selection criteria); the expected number of physicians to be surveyed; how the participants will be recruited; how and when the surveys will be administered; and an explanation of controls used to minimize bias.
- Based on the information provided, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

Decisional Review Memorandum

Date: June 16, 2008

From: Dwaine Rieves, M.D. D. Rieves 6-25-08
Director, Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products, OND, CDER

Through: Richard Pazdur, MD Pazdur
Director, Office of Oncology Drug Products

To: BL STN 125268/0 for romiplostim (Nplate)

Subject: Risk Evaluation and Mitigation Strategy

This memorandum documents the basis for my decision, in consultation with the Office of Surveillance and Epidemiology to require a Risk Evaluation and Mitigation Strategy (REMS) for romiplostim (Nplate), to be licensed under the biologics license application referenced above, approved under section 351 of the Public Health Service Act.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved:
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that Nplate is associated with five major risks signaled during the clinical development of romiplostim: 1) risk for hematologic malignancy; 2) risk for marrow fibrosis; 3) risk for hemorrhage following discontinuation of romiplostim due to worsened thrombocyotpenia than was present at baseline; 4) thrombotic/thromboembolic complications due to excessive platelet counts; 5) medication errors from concentrated drug that may result in overdosage (with risks for thrombotic/thromboembolic complications). We determined that a REMS is necessary to

ensure that the benefits of Nplate outweigh its risks. In reaching this determination, we considered the following:

A. The estimated size of the population likely to use the drug involved:

The prevalence rate of chronic (adult) immune thrombocytopenic purpura (ITP) ITP was estimated at 24 cases per 100,000 persons or 52,700 adult cases in the United States based on the 2005 census estimates. This prevalence (published in International Society on Thrombosis and Haemostasis by Feudjo-Tepie et al in 2008) was based upon analyses of the Integrated Healthcare Information System (IHCIS) database, one of the largest US health care managed databases. McMillan (Ann Intern Med: 1997) estimates that 30% of chronic ITP cases are "refractory" and this subset is the group of patients who are most likely to receive romiplostim. Hence, approximately 16,000 patients in the US (based on 2005 census) are general candidates for romiplostim therapy, as indicated.

B. The seriousness of the disease or condition that is to be treated with the drug:

Romiplostim is indicated to treat a very serious stage of chronic ITP that is generally regarded as so serious that patients are at imminent risk of death due to hemorrhage.

C. The expected benefit of the drug with respect to such disease or condition:

Romiplostim has been shown to be effective in approximately 60% of the treated chronic ITP patients. This treatment effect is a remarkable response since these patients had failed most (if not all) prior therapies. The specific treatment benefit is an increase in blood platelet counts to a level that lessens the risk for serious hemorrhage.

D. The expected or actual duration of treatment with the drug:

Romiplostim therapy is anticipated as life-long (many years) therapy for many patients since the indicated patient population is one that generally has no other long term therapeutic options and chronic ITP rarely spontaneously resolves.

E. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

The serious adverse events signaled in the clinical development of romiplostim are risks for hematologic malignancy and bone marrow fibrosis. Romiplostim also has potentially serious risks due to the thrombotic/thromboembolic risks associated with excessive platelet counts (as may occur either due to medication errors or as patient-specific responses to the drug) as well as the potentially worsened thrombocytopenia that may occur following discontinuation of the drug.

The worsened thrombocytopenia has been hypothesized as due to suppression of intrinsic thrombopoietin (TPO) levels by romiplostim therapy.

The background incidence of hematologic malignancy, bone marrow fibrosis or thrombosis in chronic ITP is not known, since most patients either respond to initial therapy with prednisone or require more aggressive immunosuppressive medications or splenectomy and these therapies may alter the risks. In a long term (median of 92 months), follow-up study of 402 patients who underwent splenectomy (the patient population potentially at greatest risk for malignancy or marrow fibrosis), only 2% of patients experienced thromboses, malignancy occurred in 3%, and marrow fibrosis was not reported (Haematologica 2005: 90 (1); Vianelli et al). Together these data suggest that the risk for marrow fibrosis, malignancy and thrombosis are relatively low within the subset of patients who undergo splenectomy for chronic ITP.

F. Whether the drug is a new molecular entity:

Romiplostim is a new molecular entity and will be the first member of the class of TPO mimetic agents approved by the FDA.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Under 21 CFR 208, the sponsor is responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed romiplostim (Nplate). Pursuant to 21 CFR Part 208, FDA has determined that romiplostim (Nplate) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of romiplostim (Nplate). FDA has determined that romiplostim (Nplate) is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, romiplostim (Nplate).

The elements of the REMS will be a Medication Guide, communication plan, elements to assure safe use (including that healthcare prescribers are specially certified, that practioners and hospitals/institutions that dispense the drug are specially certified, and that the drug be dispensed to patients with evidence or other documentation of safe-use conditions), an implementation system, a timetable for submission of assessments, and assessments of the REMS.

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Rockville, MD 20852
Tel. 301-827-1274

Memorandum

Label Review

Application Number: STN 125268/0

Name of Drug: **Romiplostim**

Sponsor: **Amgen Inc.**

Material Reviewed: Nplate (romiplostim) carton and container labels

Submission Date: October 23, 2007

OBP Receipt Date: November 16, 2007

OBP Receipt Date: February 21, 2008

OBP Revision: May 14, 2008

Background: Romiplostim is a recombinant non-glycosylated 59 kDa thrombopoietic protein produced in *E coli*. It is a fusion protein which Amgen has termed a peptibody. The peptibody molecule is comprised of a human immunoglobulin IgG1 Fc domain, with each single chain subunit covalently linked at the C-terminus to a peptide chain containing two thrombopoietin receptor binding domains (TRBD). Romiplostim stimulates platelet production by a mechanism similar to that of endogenous thrombopoietin (eTPO); however there is no sequence homology between romiplostim and eTPO. Its proposed indication is for treatment of idiopathic thrombocytopenia purpura (ITP).

Labels Reviewed: Nplate (Romiplostim) carton label
Nplate (Romiplostim) container label

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_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Risk 1

Conclusions and Recommendation:

The following deficiencies were noted in the initial review of the romiplostim vial and package labels:

-
- Bar codes should be added to both carton and container labels.
- Please indicate the purpose of the semi-circular pattern on the carton label, as it partially obscures critical information.
- The strength of the product shown on the vial and carton labels should be indicated in mcg units

Amendment:

The final revision for the Nplate (romiplostim) container and carton labels were submitted under Amgen's letters dated March 28, 2008 and April 3, 2008. These revised labels were reviewed and found acceptable under the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.1 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57 and 21 CFR 200.100

Vivian Wang
Biologist
CDER/OPS/OBP/DTP

Concurrence:

David Frucht
CMC Reviewer, CDER/OPS/OBP/DMA

Kathleen A. Clouse, Ph.D.
Director
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Sciences
Center for Drug Evaluation and Research

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X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Risk 2

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 2, 2008
To:	Rafel Dwaine Rieves, M.D, Acting Director Division of Medical Imaging and Hematology Products
Through:	Jodi Duckhorn, M.A., Team Leader Patient Labeling and Education Team Division of Risk Management (DRISK)
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Patient Education and Labeling Team Division of Risk Management (DRISK)
Subject:	Review of Patient Labeling
Drug Name(s):	Nplate (ramiplostim)
Application Type/Number:	BLA 125268
Applicant/sponsor:	Amgen, Incorporated
OSE RCM #:	2007-2248

1 INTRODUCTION

Amgen, Incorporated submitted a Biologics Licensing Application, BLA 125268/0 for Nplate (ramiplostim) on October 23, 2007. Nplate is indicated for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenia purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy.

The sponsor originally proposed a Patient Package Insert (PPI) for Nplate. The review division has determined that a Medication Guide is necessary for safe and effective use of Nplate.

The Agency has also determined that under the Title IX of Subtitle A of the Food and Drug Administration Amendments Act (FDAAA), Nplate will be required to have a Risk Evaluation and Mitigation Strategy (REMS). The Risk Mangement Team in OSE is preparing a separate review of the sponsor's REMS proposal. The review division requested that the Patient Labeling and Education Team review the sponsor's proposed Medication Guide. This review is written in response to the review division's request.

2 MATERIAL REVIEWED

- Nplate (ramiplostim) Professional Information (PI) submitted to the review division on April 24, 2008 in response to FDA comments dated April 22, 2008.
- Nplate (ramiplostim) Medication Guide submitted to the review division on April 24, 2008 in response to FDA comments dated April 22, 2008.

3 DISCUSSION

The purpose of Medication Guides is to enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level).

In our review of the MG, we have:

- simplified wording where possible,
- made it consistent with the Professional Information,
- removed unnecessary or redundant information
- ensured that the Medication Guide meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4 CONCLUSIONS AND RECOMMENDATIONS

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2.

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5.

Please let us know if you have any questions.

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_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Risk 3

Cc List:

Division of Hematology and Medical Imaging:
Rafel Dwaine Rieves
Florence Moore

Division of Risk Management:
Claudia Karwoski
Mary Dempsey
Jodi Duckhorn
Sharon Mills
Janet Anderson
Nancy Carothers
Marcia Britt
Suzanne Berkman

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 21, 2008
To:	Rafel Rieves, MD, Acting Director, Division of Medical Imaging and Hematology, HFD-160
Thru:	Kellie Taylor, Pharm D, MPH, Team Leader 3/21/08 Denise Toyer, Pharm D, Deputy Director 3/21/2008 Division of Medication Error Prevention, HFD-420
From:	Richard Abate, RPH, MS, Safety Evaluator 3/21/08 Division of Medication Error Prevention, HFD-420
Subject:	Label and Labeling Review for Nplate 500 mcg and 250 mcg
Drug Name(s):	Nplate (Romiplostim) for Injection
Application Type/Number:	BLA# 125268
Applicant/sponsor:	Amgen, Inc.
OSE RCM #:	2008-494

1 INTRODUCTION

The Division of Medication Error Prevention reviewed the labels and labeling for Nplate (romiplostim) in OSE review # 2007-2249 and forwarded our comments and recommendations to the Division of Medical Imaging and Hematologic Products on January 8, 2008. Our comments were forwarded to the Applicant in an Information Request letter dated February 26, 2008

The Applicant submitted an amendment March 11, 2008 which provided responses to this Division's comments as well as revised container labels and carton labeling.

2 MATERIAL REVIEWED

The Medication Error Staff reviewed the Applicant's revised Container Labels and Carton Labeling provided to the Agency March 11, 2008 (see Appendix A).

3 DISCUSSION

The Applicant revised the container labels and carton labeling addresses the recommendations the Medication Error Staff in our original review with two exceptions.

First, the Applicant continues to use a colored dot containing a supplemental expression of the strength to the left of the proprietary and proper names. The Medication Error Staff acknowledges the dots are consistent with the use of the color in the container labels and carton labeling (red for the 250 mcg vial and blue for the 500 mcg vial) and may assist healthcare practitioners in distinguishing the strengths of the product from one another. Thus, we have no further concerns regarding this issue.

Second, the Applicant stated in their response cover letter, "The 'N' in Nplate does not stand for anything," The Medication Error Staff We addressed the question of whether the 'N' in Nplate could state for 'normal' or 'normalizing' in evaluation of the proprietary name (OSE review #2007-2549, dated February 27, 2008.) We noted this concern would be minimized . In addition, the Medication Error Staff noted in OSE review #2007-2249 the use difficult to read, and the product could be arranged in the refrigerator of a pharmacy under 'P' for 'Plate' rather than 'N' for 'Nplate'.

4 CONCLUSIONS AND RECOMMENDATIONS

4.1 COMMENTS TO THE APPLICANT

Revise the container labels and carton labeling using one color in the presentation of the proprietary name.

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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Risk 4

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

MEMORANDUM

****PRE-DECISIONAL AGENCY MEMO****

Date: **February 28, 2008**

To: **Florence Moore, Project Manager**
Division of Medical Imaging and Hematology Drug Products

From: **Sean Bradley, Regulatory Review Officer**
Division of Drug Marketing, Advertising, and Communications

Subject: **BLA 125268**
Romiplostim
Proposed Product Labeling

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the proposed product labeling for Romiplostim and have the following comments. The proposed labeling dated January 14, 2008, was compared to the label of the previously approved product Solaris. DDMAC comments are in italics and suggested edits are in **bold underlined text** and ~~strike-through~~.

2.1 Recommended Dosage Regimen, ***Dose Adjustments***

2.2 Preparation and Administration

2.3 Use of Nplate with Concominant Medical ITP Therapies

If you have any questions or comments, please contact Sean Bradley at 301-796-1332 or sean.bradley@fda.hhs.gov

3. DOSAGE FORMS AND STRENGTHS.

6.1 Clinical Studies Experience,

6.1 Bleeding Events

11 DESCRIPTION

14 CLINICAL STUDIES, Studies 1 and 2

16 HOW SUPPLIED/STORAGE AND HANDLING

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 8, 2008
To:	Rafel Rieves, MD Acting Director, Division of Medical Imaging and Hematology, HFD-160
Thru:	Kellie Taylor, Pharm D, MPH, Team Leader 1/9/08 Denise Toyer, Pharm D, Deputy Director 1/9/08 Carol Holquist, RPh, Director 1/9/08 Division of Medication Errors and Technical Support, HFD-420
From:	Richard Abate, RPh, MS, Safety Evaluator 1/9/08 Division of Medication Errors and Technical Support, HFD-420
Subject:	Label and Labeling review for Nplate (romiplostim) 500 mcg and 250 mcg
Drug Name(s):	Nplate (Romiplostim)
Application Type/Number:	BLA# 125268
Applicant/sponsor:	Amgen, Inc.
OSE RCM #:	2007-2249

CONTENTS

EXECUTIVE SUMMARY

DMETS reviewed the proposed container labels and labeling for Nplate (romiplostim) to identify potential safety issues related to medication errors. Our analysis identified deficiency in the way the established name is expressed and how the strength is expressed to be our main concerns. The expression of the established name as "subcutaneous injection," was noted as incongruent with USP standards for injectable medications. In addition, DMETS' analysis also finds the proposed container labels and labeling introduce other vulnerabilities that could lead to medication errors. DMETS' recommendations for label and labeling modifications are found in Section 6.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Medical Imaging and Hematology to evaluate the labels and labeling for 250 mcg and 500 mcg Nplate (romiplostim).

1.2 PRODUCT INFORMATION

Nplate is an Fc-peptide fusion protein that increases platelet production. Nplate (romiplostim) is indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia purpura who have a spleen and do not respond to corticosteroids or immunoglobulin or have had a splenectomy.

The starting adult dose of Nplate is 1 mcg/kg given subcutaneously once weekly. The dose is adjusted to achieve and maintain a platelet count of 50 x 10^9/L The doses ranged during clinical trials from 1 mcg/kg to 7 mcg/kg with median doses of 2 mcg/kg for patients with a spleen and 3 mcg/kg for patients post splenectomy. The maximum dose of Nplate is 10 mcg/kg given subcutaneously once weekly.

Nplate vials are available in two strengths, 250 mcg and 500 mcg. The product is a lyophilized cake requiring reconstitution with sterile water for injection prior to administration. The 250 mcg vial is reconstituted with 0.72 mL of sterile water to achieve an extractable solution of 250 mcg/0.5 mL. The 500 mcg vial is reconstituted with 1.2 mL of sterile water to achieve an extractable solution of 500 mcg/mL.

2 METHODS AND MATERIALS

The Sponsor submitted draft container label, carton labeling, and insert labeling on October 23, 2007. See Appendix A for draft container labels and carton labeling.

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton and container labels communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[1]

Because DMETS staff analyze reported misuse of drugs, DMETS staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. DMETS uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

3 RESULTS

3.1 CONTAINER LABELS AND CARTON LABELING

Upon review of the carton labeling and container labels, DMETS notes the product strength is expressed as a concentration (i.e., 250 mcg/0.5 mL and 500 mcg/1 mL), yet this lyophilized product is not a solution until after reconstitution.

Lastly, DMETS notes the strengths are distinguished using only blue and red circular backgrounds behind the strengths in the same white font and the font is very small on the container label. See Appendix A.

3.2 PACKAGE INSERT LABELING

Upon review of the package insert labeling, DMETS notes "Subcutaneous Injection" appears in the established name for a lyophilized product which requires reconstitution prior to administration.

4 DISCUSSION

4.1 CONTAINER LABELS AND CARTON LABELING

In review of the container labels and carton labeling, DMETS noted several potential sources for medication errors.

The expression of the strength as a concentration implies to the user that the product is already in solution when in fact this product is lyophilized and requires reconstitution prior to administration. DMETS is

[1] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

concerned that when dispensing the product in an inpatient setting, a pharmacist may dispense the dispensing pack to the floor without reconstituting because they think it is already in solution. The product should be prepared aseptically in an IV admixture room prior to leaving the pharmacy. In addition, if the product is reconstituted with an incorrect volume, DMETS believes the expression of the strength as a concentration will likely increase the potential for the user to calculate and administer the wrong dose.

We also noted concerns with the volumes required for product dilution. Each strength of Nplate requires a specific volume of diluent to achieve the same concentration (0.72 mL for 250 mcg/0.5 mL vs. 1.2 mL for 500 mcg/mL). In addition, these volumes are not the same ratio of diluent to the vial strength (0.72 mL compared to 1.2 mL vs. 250 mcg compared to 500 mcg). As a patient requires dose escalation to achieve and maintain platelet counts, the healthcare provider will likely be using a 250 mcg vial initially for a patient then change to a 500 mcg vial as the dose increases. Healthcare providers may miscalculate the volume required to reconstitute the 500 mcg vial as twice the amount needed to reconstitute the 250 mcg vial which could lead to an incorrect concentration and an under dose of Nplate.

The container label and carton labeling look nearly identical due to the trade dress of the sponsor. (See Appendix A.) The sponsor chose to use red and blue circular backgrounds behind an additional strength set off to the left of the proprietary name to distinguish one strength from another. DMETS believes this dot of color is likely to be overlooked by healthcare providers leading to selection errors.

DMETS also notes the background color for the trade dress is a fading gradient color of blue. This shade of blue is not identical to the color of the font used in the proprietary name but similar. However, DMETS believes the similarity of the color makes the proprietary name difficult to read as the two different shades of blue and thus does not provide enough contrast to make the proprietary name clear.

Furthermore, the red font utilized in the proprietary name appears to be the same color behind the supplementary expression of the strength 250 mcg. The sponsor's attempt to differentiate the strengths using red and blue is limited by the use of the same color fonts in the proprietary name. DMETS believes a healthcare provider will likely see the red font of the proprietary name on a 500 mcg vial of Nplate and mistakenly associate that red font with the 250 mcg strength vial thus leading to a selection error of the wrong strength. Although the sponsor uses colors that may seem to differentiate the strengths, the fact that the same color fonts appear in the proprietary name increase the potential risk for the strengths to be confused.

4.2 PACKAGE INSERT LABELING

The established name in the labeling includes "subcutaneous injection" which is incongruent with the actual Nplate product which is a lyophilized product. The U.S Pharmacopeia states Biologics that are intended to be administered by injection should comply with the requirements for Labeling under

Injections.[2] The dosage form "injection" denotes a product defined by the U.S Pharmacopeia as liquid preparations that are drug substances or solutions thereof.[3] This product is not a liquid preparation. Generally, the nomenclature for a lyophilized product would use the term "For Injection."

5 CONCLUSIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. DMETS believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

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[2] U.S. Pharmacopeia 30, General Chapters (1041) Biologics, 2007

[3] U.S. Pharmacopeia 30, General Chapters (1) Injections, 2007

[4] www.ismp.org, "ISMP's List of Error Prone Abbreviations, Symbols, and Dose Designations," The Institute of Safe Medication Practices, 2006.

[5] www.jointcommission.org, Official Do Not Use List, The Joint Commission, 2007.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Sponsor to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

6 RECOMMENDATIONS

We recommend the revisions below be implemented in the interest of minimizing user error and maximizing patient safety. DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any communication to the sponsor with regard to this review. If you have any questions or need clarification, contact Janet Anderson, project manager, at 301-796-0675.

6.1 CONTAINER LABELS AND CARTON LABELING

6.1.1 DMETS recommends expressing the strength as mcg rather than as a concentration.

6.1.2 DMETS recommends using only one color in the name of the product for continuity and clarity on the labels and labeling.

6.1.3 If space allows on the container label, DMETS recommends the sponsor attempt to distinguish the expression of strength beneath the established name

6.1.4 DMETS recommends

6.1.5 DMETS recommends improving the contrast of the proprietary name from the background of the trade dress to improve readability.

6.2 PACKAGE INSERT LABELING

6.2.1 DMETS recommends revising the established name to the more appropriate, "For Injection," to comply with USP standards.

6.2.2

6.2.3

approved products.

6.2.4 DMETS recommends eliminating the vial size or fill volume (5 mL) from the labeling to reduce the potential for errors involving reconstitution and dose calculation.

6.3 COMMENTS TO THE SPONSOR

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. DMETS believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides the following recommendations that aim at reducing the risk of medication errors.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Sponsor to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

6.3.1 Container Labels and Carton Labeling

6.3.1.1 DMETS recommends expressing the strength as mcg

6.3.1.2 DMETS recommends using only one color in the name of the product for continuity and clarity on the labels and labeling.

6.3.1.3 If space allows on the container label, DMETS recommends the sponsor attempt to distinguish the expression of strength beneath the established name

6.3.1.4 DMETS recommends

6.3.1.5 DMETS recommends improving the contrast of the proprietary name from the background of the trade dress to improve readability.

6.3.2 Package Insert Labeling

6.3.2.1 DMETS recommends revising the established name to the more appropriate, "For Injection," to comply with USP standards.

6.3.2.2 DMETS recommends expressing the strength of the product consistently throughout the labeling to reduce the potential for confusion between mg and mcg.

6.3.2.3 DMETS recommends eliminating the use of trailing zeroes throughout the labeling.

__3__ Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Risk 5

21 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Risk 6