

SUPPLEMENT TO BACKGROUND INFORMATION

FOR

THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

UPDATE TO ROMIPLOSTIM RISK MANAGEMENT PROGRAM PROPOSAL

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1. Key Points

- Amgen is committed to establishing a comprehensive risk management program, including a formal restricted distribution program, as a component of the Risk Minimization Action Plan (RiskMAP) for romiplostim. Amgen is referring to this as controlled distribution.
- The goals of the Romiplostim Management Program (name to be determined) are appropriate (on-label) use of romiplostim in treating thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP), and to assess the risks associated with the use of romiplostim. The objectives are to educate patients and physicians about romiplostim's risk profile and appropriate use; limit off-label use; and monitor, track, and assess identified and potential risks of romiplostim in patients with chronic ITP.
- The proposed Romiplostim Management Program has the following highlights:
 - Specialist physicians (hematologists or hematologists/oncologists) will identify patients with chronic ITP for the Romiplostim Management Program, and will review with them romiplostim's benefits and risks and the Medication Guide.
 - Patients will sign the Program Enrollment Questionnaire providing consent to the exchange of their medical information and the enrollment into the program and certifying their review of the Medication Guide. The physician will provide the Program Enrollment Questionnaire to the program Case Manager to initiate the controlled distribution process.
 - The Case Manager will review the Program Enrollment Questionnaire to check the physician certification of diagnosis of chronic ITP and authorize shipment. This is reconfirmed at the first 6 month time point only.
 - The physician will order romiplostim from a wholesaler, who will pass the order to the case management vendor; the case management vendor will arrange to ship the order to the physician.
 - During treatment, the Case Manager will collect safety information on identified and potential risks from the physician every 6 months using a designated collection tool (the Safety Questionnaire), and will facilitate ongoing drug shipment.
 - Safety and utilization data collected by the Case Managers will be entered into a tracking database; events will, as applicable, trigger communication with Amgen Global Safety for follow-up actions such as testing for neutralizing antibodies and adverse event reporting to the FDA.

2. Identified and Potential Risks of Romiplostim

Based on experience in pre-clinical and/or clinical studies, and in light of what is known about thrombopoiesis, the following identified and potential risks have been determined for romiplostim in the setting of chronic ITP:

Identified Risks

- Re-occurrence of thrombocytopenia after cessation of treatment
- Increased bone marrow reticulin

Potential Risks

- Thrombotic / thromboembolic complications
- Neutralizing antibodies that cross react with endogenous thrombopoietin (eTPO)
- Progression of existing hematopoietic malignancies or myelodysplastic syndrome (MDS)
- Progression of increased reticulin to an irreversible bone marrow fibrotic state
- Off-label use in indications where risk-benefit ratio has not been adequately studied
- Medication errors due to the potency of romiplostim and the small volumes administered.

Amgen is committed to setting risk management tools in place to manage these identified and potential risks, including a formal Risk Minimization Action Plan (RiskMAP).

3. Introduction – Risk Management Plan and RiskMAP

The Risk Management Plan (RMP) is composed of Risk Assessment and Risk Minimization activities. Risk Assessment is performed through pharmacovigilance as well as clinical and observational studies. Risk minimization activities for romiplostim include pharmacovigilance, targeted studies, and a RiskMAP.

The RiskMAP is a strategic safety program designed to meet specific goals and objectives in minimizing product risks while preserving benefits. Activities of the

RiskMAP go beyond FDA-approved labelling. The RiskMAP is designed to employ tools that are evidence-based, allow appropriate product access, and consider stakeholder input, technology, practice settings, and other factors. In developing a RiskMAP for romiplostim, Amgen consulted the Guidance for Industry: Development and Use of Risk Minimization Action Plans. US Department of Health and Human Services, March 2005.

The RiskMAP tools for romiplostim are of 3 categories: targeted education and outreach, reminder systems, and controlled distribution. The effectiveness of these tools will be monitored and periodically reported to the FDA.

4. Overview of Romiplostim RiskMAP

The goals of the RiskMAP are appropriate (on-label) use of romiplostim to treat thrombocytopenia in patients with chronic ITP, and to assess the risks associated with the use of romiplostim. The objectives of the RiskMAP are:

- To educate patients and physicians about romiplostim's risk profile and appropriate use;
- To limit off-label use;
- To monitor, track, and assess identified and potential risks of romiplostim in patients with chronic ITP.

Amgen has engaged hematology/oncology practitioners and the FDA with this proposal and will continue to seek feedback during continued development of this program.

An overview of the tools that will be used in the romiplostim RiskMAP is provided below.

Targeted Education and Outreach

- Product Labelling/Medication Guide
- Provider Education and Training Kit

Reminder Systems

- Medication Guide
- ITP Diagnosis Checklist
- Romiplostim Management Program Enrollment Questionnaire (Attachment 1)

Controlled distribution

- Physician certification of diagnosis of chronic ITP and patient consent are required to receive romiplostim through the Romiplostim Management Program;
- Ships only to physicians for the treatment of enrolled chronic ITP patients
- Tracking database (safety and utilization).

These elements are designed to:

- Ship product only to prescribing physicians who have certified the diagnosis of chronic ITP and are participating in the Romiplostim Management Program;
- Ship product only for the treatment of patients with chronic ITP;
- Provide every prescribing physician with an FDA-approved training kit containing educational materials;
- Provide every new patient with a Medication Guide;
- Coordinate reimbursement by insurers as means of offering program value to physicians;
- Enroll all patients in a tracking database (safety and utilization).

5. Romiplostim Management Program

Central to the romiplostim RiskMAP will be controlled distribution of drug. Romiplostim will be shipped only to physicians who certify diagnosis of chronic ITP, whose patients have provided specific consent to participate in the Romiplostim Management Program, have been educated about romiplostim's risk profile, and who will be assigned a Case Manager to track their utilization and safety information.

Access to Romiplostim Management Program (Initiation of Treatment):

- Physicians identify patients with chronic ITP who are appropriate candidates for romiplostim therapy.
- The physician will review romiplostim's risks and benefits with the patient and reviews the Medication Guide. The Medication Guide will have been provided to

physicians by Amgen sales representatives and is also available through the branded website.

- The physician will complete a Program Enrollment Questionnaire (Attachment 1) certifying a diagnosis of chronic ITP. Information to be collected on the questionnaire includes:
 - Patient identifiers
 - Physician certification of prescribing romiplostim for the treatment of chronic ITP as described in the prescribing information
 - Patient confirmation of review of Medication Guide and discussion of risks and benefits with the physician
 - Patient consent to enrollment in the Romiplostim Management Program.
- Both patient and physician will sign the form. The physician's signature certifies the diagnosis of chronic ITP, and the patient's signature confirms agreement to enroll into the Romiplostim Management Program and confirms review of Medication Guide and discussion of risks and benefits with the physician.
- The physician will then provide the completed form to the Romiplostim Management Program to initiate the program.
- On receipt of the Program Enrollment Questionnaire, the Case Manager will check for completeness including physician certification of diagnosis of chronic ITP.
- The Case Manager authorizes drug shipment when the physician orders product from the physician's preferred wholesaler; the wholesaler, who does not have romiplostim, passes the order to the case management vendor; the wholesaler invoices the physician; the case management vendor arranges to ship product to the physician. The single point of inventory is at the case management vendor.
- At this point the Case Manager also arranges shipment of a Provider Education and Training Kit to the Physician.

Continued Access to Romiplostim Management Program (Continuation of Treatment):

- When the physician reorders romiplostim, the Case Manager will check to confirm that the patient has already enrolled in the Romiplostim Management Program and then authorize the shipment. At the first 6 month time point only, the Case Manager will confirm that the patient's diagnosis remains chronic ITP, and will approve drug shipment upon confirmation.
- Multiple vials may be shipped for a single patient at a given time. No additional forms are required to be completed for these shipments.
- The Case Manager will collect safety information from the physician every 6 months using a designated collection tool, the Safety Questionnaire (Attachment 2).
- Patient data will be entered into a tracking database (safety and utilization). Amgen Global Safety will review the database and process adverse events according to standard procedures.

6. Details of the Romiplostim Management Program Tools

The following sections provide additional detail regarding the tools proposed for the Romiplostim Management Program.

6.1 Targeted Education and Outreach

Objectives of the Provider Education and Training Kit are to provide prescribers with an FDA-approved integrated kit containing essential information, warnings, and support materials; provide support to hematologists or hematologists/oncologists to aid in correctly diagnosing chronic ITP and using romiplostim according to the label.

Amgen will distribute the Provider Education and Training Kits to new prescribers by mail. The provision of this kit will be documented.

Contents of the Provider Education and Training Kits will include:

- FDA-approved educational materials on ITP and risk factors of romiplostim;
- Pre-Use Checklist;

- ASH guidelines, which will provide additional information on diagnosis of ITP, and includes guidance on bone marrow biopsies in ITP patients;
- Medication Guide: the Medication Guide will be directly distributed to physicians to be given to patients as part of the program;
- Patient disease state educational brochure: A tool that will educate patients on chronic ITP and questions they should ask their physician.

6.1.1 Product Labelling/Medication Guide

FDA-approved prescribing information remains the foundation of risk management. The risks of romiplostim are managed in part through instructions in the Warnings and Precautions section of the prescribing information. In addition, the Medication Guide presents information on the risks of romiplostim in patient-friendly language, which the physician will review with each patient; this discussion will be documented before shipment and administration of the first dose of romiplostim.

6.1.2 Tracking Database (Safety and Utilization)

Each patient providing consent to participate in the Romiplostim Management Program will be entered into the tracking database (safety and utilization). The Case Manager will collect safety information from the physician every 6 months using a designated collection tool, the Safety Questionnaire (Attachment 2). This questionnaire will include confirmation that the patient's diagnosis remains chronic ITP.

6.2 Reminder Systems

6.2.1 Pre-use Checklist

The pre-use checklist is to remind clinicians of romiplostim safety warnings (as listed in the prescribing information) and of the key points of patient assessment prior to administering romiplostim. It is anticipated that physicians will routinely use the checklist to assist in proper diagnosis of chronic ITP. The pre-use checklist will be distributed in every training kit.

6.2.2 Medication Guide

Before patients receive romiplostim, they will be informed of the risks and benefits of romiplostim use through a discussion and review of the Medication Guide with the

physician, which will be documented. A copy of the Medication Guide will be provided with each shipment of romiplostim. Finally, the medication guide will also be included in the Provider Education and Training Kits.

6.2.3 Safety Questionnaire

The Case Manager will use a designated data collection tool (the Safety Questionnaire) to obtain patient safety data on identified and potential risks every 6 months. Patient data will be entered into a tracking database (safety and utilization). Amgen Global Safety will review the database and process adverse events according to standard procedures.

6.3 Controlled Distribution

The Romiplostim Management Program is described in [Section 5](#).

7. Metrics and Effectiveness Analysis

Metrics will be established to measure and evaluate the effectiveness of each of the tools of the proposed RiskMAP. The effectiveness of RiskMAP activities will be monitored and assessed on an ongoing basis. In addition, Amgen proposes targeted studies to assess effectiveness. Revisions to the RiskMAP program will be considered and discussed with the Agency.

8. Conclusions

Romiplostim is an important advance in the treatment of chronic ITP. Identified and potential risks associated with romiplostim will be managed through a comprehensive risk management program. Prescribing information, active surveillance, targeted studies, and a formal RiskMAP comprise this program. The proposed RiskMAP includes targeted education and outreach, reminder systems, and controlled distribution. The objectives of the RiskMAP are patient and physician education on romiplostim's risk profile and appropriate use in chronic ITP; minimization of off-label use; and monitoring, tracking and assessing identified and potential risks associated with romiplostim. Amgen believes the proposals outlined in the RiskMAP as part of the RMP are appropriate and adequate to manage and minimize the risks of romiplostim.

Attachment 1. Draft Program Enrollment Questionnaire

 Program Enrollment Questionnaire
1. Patient Information and Physician Certification of Diagnosis
Patient Name: _____ Age: _____ Gender: <input type="checkbox"/> M <input type="checkbox"/> F Weight: _____ kg
*Romiplostim is a thrombopoietin (TPO) mimetic indicated for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP): <ul style="list-style-type: none">• Who are non-splenectomized and have an insufficient response or are intolerant to corticosteroids and/or immunoglobulins.• Who are splenectomized and have an insufficient response to splenectomy. I certify that I am prescribing Romiplostim for this patient for the treatment of chronic ITP as described in the prescribing information Prescriber's signature: _____
2. Physician Information
Full Name (print): _____ Phone: _____ e-mail: _____ Physician Signature: _____ Date: ____/____/____
3. Consent for Participation in the Romiplostim Patient Management Program
I consent being contacted by the Romiplostim case manager and to the sharing of my medical treatment information within the patient management program for Nplate® and Amgen. Patient signature _____ Date _____
4. Patient Confirmation of Medication Guide Receipt
Prior to receiving my first dose of Romiplostim therapy, my health care provider has shared with me the Romiplostim Medication Guide and patient education kit and described the benefits and risks of Romiplostim therapy. Patient signature _____ Date _____

Draft - Pending FDA Agreement - For discussion purposes only

