Initial REMS Approval: 12/2009
Most recent modification: 04/2012

KALBITOR®

BLA 125277

Dyax Corp.
55 Network Drive
Burlington, MA 01803

RISK EVALUATION AND MITIGATION STRATEGY

I GOAL

To inform healthcare providers about the risk of anaphylaxis associated with KALBITOR and the importance of distinguishing between a hypersensitivity reaction and hereditary angioedema (HAE) attack symptoms.

II RISK EVALUATION AND MITIGATION STRATEGY ELEMENTS

A. Communication Plan

In accordance with FDCA 505-1(e)(3), a communication plan will be implemented by Dyax Corp. to convey important information about the risk of anaphylaxis and that the signs and symptoms of anaphylaxis and of acute attacks of HAE may overlap.

1. The initial audience for this communication plan is healthcare providers likely to prescribe KALBITOR and treat HAE patients; including two specialties: Allergy/Immunology and Emergency Medicine.

2. The communication plan includes the Dear Healthcare Professional Letter that will describe the key risks of KALBITOR: [see attached DHCP Letter]

3. Distribution of materials: Communication plan materials will be distributed at the same time as product launch.

   Direct Mail: Dyax will issue the DHCP Letter to targeted healthcare providers at the time of product launch and yearly for 2 years thereafter. In addition, for 2 years after launch, any known new prescribers of KALBITOR not previously targeted will also be sent the DHCP Letter. The DHCP Letter will include the warnings associated with KALBITOR and will describe symptoms of anaphylaxis that may

overlap with presenting symptoms of an attack of HAE. The DHCP Letter will be sent by direct mail to providers in the specialties of Allergy/Immunology and Emergency Medicine. The DHCP Letter will include the Full Prescribing Information. Copies of these materials will also be available through a stand-alone webpage accessed through the product web site. (see attached webpage)

Dyax Representatives: The DHCP Letter will be provided with the Full Prescribing Information and Medication Guide by Dyax sales representatives to potential prescribers during the first discussion of KALBITOR during the first year of product availability.

The communication material listed in Section A.2 above will also be available at the time of approval by calling Dyax at 1-888-452-5248.

B. Timetable for Submission of Assessments

REMS assessments will be submitted at 18 months, 3 years and 7 years after initial REMS approval (December 1, 2009). The reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment time interval. Each assessment will be submitted so that it is received by the FDA on or before the due date.

[on Dyax letterhead]

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Dyax Corp. is writing to inform you of important safety information for KALBITOR® (ecallantide). KALBITOR is a subcutaneous injection indicated for treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age or older. Important safety information related to KALBITOR includes:

- The risk of anaphylaxis
- The need to distinguish signs and symptoms of anaphylaxis from HAE attacks

To ensure that the benefits of KALBITOR treatment outweigh the risks, the KALBITOR labeling includes a boxed warning concerning anaphylaxis, as follows:

WARNING: Anaphylaxis

Anaphylaxis has been reported after administration of KALBITOR®. Because of the risk of anaphylaxis, KALBITOR should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Healthcare professionals should be aware of the similarity of symptoms between hypersensitivity reactions and hereditary angioedema and patients should be monitored closely. Do not administer KALBITOR to patients with known clinical hypersensitivity to KALBITOR.

In 255 HAE patients treated with intravenous or subcutaneous KALBITOR in clinical trials, 10 patients (3.9%) experienced anaphylaxis. For the subgroup of 187 patients treated with subcutaneous KALBITOR, 5 patients (2.7%) experienced anaphylaxis. In clinical trials, when hypersensitivity was observed, it usually occurred immediately following exposure to KALBITOR, and always **within the first hour** following dosing.

In order to appropriately manage anaphylaxis, it must be recognized if it occurs. Because the signs and symptoms of HAE attacks may overlap with the signs and symptoms of anaphylaxis, there is a need to distinguish between serious hypersensitivity, including anaphylaxis and HAE attack symptoms.

Signs and symptoms that can be seen in either anaphylaxis or acute attacks of HAE include:

- erythema of the skin
- laryngeal edema
- dyspnea
- flushing
- stomach and gastrointestinal symptoms
- decreases in blood pressure

KALBITOR should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. If a patient does not respond to an initial dose of KALBITOR, an additional dose of KALBITOR may be administered within a 24 hour period; before administering a repeat dose of KALBITOR, it is very important to assess the patient to assure that symptoms are reflective of an HAE attack and not a hypersensitivity reaction.

Please take time to read the enclosed KALBITOR Package Insert for full prescribing information and to review the Medication Guide with patients.

To report adverse events potentially associated with KALBITOR, please call Dyax Corp. at 1-888-452-5248. Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by:

- Phone at 1-800-FDA-1088 (1-800-332-1088)
- Facsimile at 1-800-FDA-0178 (1-800-332-0178)
- Mail using FDA Form 3500 located at http://www.fda.gov/medwatch

We invite you to contact Dyax Corp. at 1-888-452-5248 if you have any questions about KALBITOR or the information in this letter.

Sincerely,

Yung Chyung, M.D.
Medical Director
Dyax Corp.

Enclosures: Full Prescribing Information including Medication Guide

Dyax

KALBITOR ecallantide

IMPORTANT SAFETY INFORMATION FOR HEALTHCARE PROFESSIONALS
Risk Evaluation and Mitigation Strategy (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

In order for Dyax to communicate certain risks to ensure that KALBITOR is prescribed and taken safely, Dyax has worked with the FDA to develop materials to communicate the risk of anaphylaxis and the importance of distinguishing between hypersensitivity reactions and ongoing hereditary angioedema (HAE) symptoms. The REMS program is designed to inform healthcare providers about the potential risks with KALBITOR. To learn more about serious risks, read the important safety information provided in this link.

The goal of the KALBITOR REMS is:

- To inform healthcare providers about the risk of anaphylaxis associated with KALBITOR and the importance of distinguishing between a hypersensitivity reaction and hereditary angioedema (HAE) attack symptoms.

To download the REMS documents:

Dear Healthcare Professional Letter.pdf Prescribing Information.pdf

Important Safety Information

WARNING: Anaphylaxis

Anaphylaxis has been reported after administration of KALBITOR®. Because of the risk of anaphylaxis, KALBITOR should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Healthcare professionals should be aware of the similarity of symptoms between hypersensitivity reactions and hereditary angioedema and patients should be monitored closely. Do not administer KALBITOR to patients with known clinical hypersensitivity to KALBITOR.

CONTRADICTIONS
Do not administer KALBITOR to a patient who has known clinical hypersensitivity to KALBITOR.

WARNINGS AND PRECAUTIONS
In 255 HAE patients treated with intravenous or subcutaneous KALBITOR in clinical trials, 10 patients (3.9%) experienced anaphylaxis. For the subgroup of 187 patients treated with subcutaneous KALBITOR, 5 patients (2.7%) experienced anaphylaxis. These reactions occurred within the first hour after dosing.

Symptoms associated with these reactions have included chest discomfort, flushing, pharyngeal edema, pruritus, rhinorrhea, sneezing, nasal congestion, throat irritation, urticaria, wheezing, and hypotension.

Patients should be observed for an appropriate period of time after administration of KALBITOR, taking into account the time to onset of anaphylaxis seen in clinical trials. Given the similarity in hypersensitivity symptoms and acute HAE symptoms, patients should be monitored closely in the event of hypersensitivity reaction.

ADVERSE EVENTS
The most common adverse events (≥3% and greater than placebo) in HAE patients were headache, nausea, diarrhea, pyrexia, injection site reactions, and nasopharyngitis. There is a potential for immunogenicity with the use of KALBITOR. Patients who seroconvert may be at a higher risk of hypersensitivity reaction. The long-term effects of antibodies to KALBITOR are not known.

USAGE
KALBITOR should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Safety and effectiveness of KALBITOR in patients below 16 years of age have not been established.

Please see the Full Prescribing Information including Boxed Warning and Medication Guide.

Healthcare professionals should report all suspected adverse events associated with the use of KALBITOR. Please contact Dyax Corp. at 1-888-452-5248. Alternatively, this information may be reported to the FDA MedWatch System by phone at 1-800-FDA-1088 or by mail using Form 3500 at www.fda.gov/medwatch.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY M SEYMOUR
04/24/2012