

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125277

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Division of Pulmonary and Allergy Products

NDA/BLA #s: BLA# 125277
Products: KALBITOR, ecallantide, solution for injection
SPONSOR: Dyax Corp.
FROM: Curtis J. Rosebraugh, MD, MPH
Director, Office of Drug Evaluation II

DATE: December 1, 2009

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). 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 (NME).

During review of the BLA for Kalbitor (ecallantide) for treatment of acute attacks of hereditary angioedema, anaphylaxis was identified as a safety signal. After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Kalbitor (ecallantide) to ensure that the benefits of the drug outweigh the risks of anaphylaxis. In reaching this determination, we considered the following:

- A. Hereditary angioedema (HAE) is a rare, autosomal dominant disorder that affects approximately 1 in 10,000 to 1 in 150,000 individuals. This estimate is based upon general estimates of prevalence in the literature¹. Because of the rarity of HAE, the Kalbitor (ecallantide) program has been granted orphan drug status.
- B. Hereditary angioedema is a rare, autosomal dominant disorder that is characterized by intermittent, unpredictable attacks of subcutaneous or submucosal edema of the face, larynx, gastrointestinal tract, limbs, and/or genitalia. Attacks can be life-threatening,

¹ Nzeako UC et al. Arch Intern Med 2001; 161 (2417-2429).

particularly those attacks involving the airway. Attacks can also lead to significant morbidity, including hospitalization or even surgery for abdominal pain.

- C. There is an unmet need in the HAE community for a product to treat acute attacks. In two placebo controlled clinical trials, compared to placebo, Kalbitor (ecallantide) improved symptoms in patients with acute attacks of HAE.
- D. If approved, Kalbitor (ecallantide) would be expected to be used widely in the HAE population. Since HAE attacks are unpredictable and occur intermittently, Kalbitor (ecallantide) has the potential for chronic intermittent use. It is possible that some patients could use Kalbitor (ecallantide) on an intermittent basis for their lifetime.
- E. Kalbitor (ecallantide) is a therapeutic protein and is immunogenic, which predisposes to hypersensitivity reactions. Anaphylaxis was noted as a safety signal in the clinical program submitted to support the efficacy and safety of Kalbitor (ecallantide). Anaphylaxis is a severe, potentially fatal, systemic allergic reaction. Using diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis², 9 potential cases of anaphylaxis were identified out of 243 HAE patients treated with Kalbitor (ecallantide), for an anaphylaxis rate of 3.7%. Most of these reactions occurred following repeat dosing of Kalbitor (ecallantide).

Regarding a background rate of anaphylaxis in this population, anaphylaxis is an event that occurs following contact with an allergy-causing substance. Patients would not normally have anaphylaxis as an event unless coming into contact with an allergen. Many of the HAE symptoms are similar to anaphylaxis, which could make it difficult to determine if an anaphylaxis event occurs. The rate of anaphylaxis in the ecallantide clinical program may be an underestimate because of the overlapping of symptoms of HAE attacks and anaphylaxis.

- F. Kalbitor (ecallantide) is a new molecular entity.

Please see also REMS memoranda dated March 25, 2009, and October 16, 2009 for relevant background regarding our determination that a REMS is necessary for this drug.

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. FDA has determined that Kalbitor (ecallantide) 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 Kalbitor (ecallantide). FDA has determined that ecallantide is a product that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use Kalbitor (ecallantide).

The elements of the REMS will be a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

² Sampson HA et al. J Allergy Clin Immunol 2006; 117:391-7.



Curtis Rosebraugh, M.D., M.P.H
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research



**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: December 1, 2009
To: Badrul Chowdhury, M.D., Director
Division of Pulmonary and Allergy Products
Thru: Mary Willy, PhD, Deputy Director
Division of Risk Management (DRISK)
From: **OSE Kalbitor Review Team**

*Mary Willy
Deputy Director
12/1/09*

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Subject: Review of REMS received December 1, 2009
Drug Name(s): Kalbitor (ecallantide)
Application Type/Number: BLA 125277
Applicant/sponsor: Dyax Corp
RCM #: 2009-103

1 INTRODUCTION

This review responds to the request by the Division of Pulmonary and Allergy Products (DPAP) for the Office of Surveillance and Epidemiology's (OSE) Division of Risk Management (DRISK) to review and comment on the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS) for ecallantide (Kalbitor).

2 BACKGROUND

Ecallantide, trade name Kalbitor, has a proposed indication for treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older. Kalbitor is a plasma kallikrein inhibitor and a new molecular entity. It is administered as a subcutaneous injection (SC); the recommended dosage is a 30 mg dose administered in three 10 mg injections. A repeat dose of 30 mg may be administered within 24 hours if an attack persists.

Hereditary angioedema is a rare, autosomal dominant disorder that affects about 1 in 10,000-50,000 individuals worldwide; it is considered an orphan disease. Acute attacks of HAE are potentially life-threatening, especially if the airway is compromised by laryngeal edema. When the BLA 125277 application was submitted, there were no treatment options available for acute attacks of HAE although treatments for prophylaxis and chronic therapy are available. The current standard of care is supportive therapy to treat the symptoms (pain, nausea, airway obstruction).

The primary safety concern with Kalbitor is anaphylaxis. In 255 HAE patients treated in clinical studies with intravenous (IV) or SC Kalbitor, 10 patients (3.9%) experienced anaphylaxis. For the subgroup of 187 patients treated with SC 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.

Because HAE attacks are variable in both frequency and location between individuals and even within a given individual, the course can be unpredictable. In light of this factor, the safety issue related to anaphylaxis becomes more serious due to the possibility that a provider may misdiagnose an anaphylactic reaction upon exposure to Kalbitor as worsening of an HAE attack involving laryngeal edema. The concern is that a provider gives additional doses of Kalbitor when the patient needs to be treated for anaphylaxis.

In addition to the risk of anaphylaxis, the Pulmonary-Allergy Drugs Advisory Committee (PADAC) felt that specific safety measures were needed such as: a concerted effort to educate institutions and patients of the anaphylaxis risk with the drug; stronger precautions warning about anaphylaxis; recommendation that injections be given in an appropriate setting to monitor hypersensitivity reactions; and comprehensive education regarding monitoring of drug after injection. These concerns initially prompted OSE and DPAP to recommend a REMS with a Medication Guide (MG), Communication Plan (CP) and Elements to Assure Safe Use (ETASU). A Complete Response (CR) letter was sent to the sponsor March 25, 2009 requiring a REMS with MG, CP and ETASU to ensure that the benefits of the drug outweigh the risk of anaphylaxis. In response to the CR letter, the sponsor submitted a REMS for BLA 125277 on June 1, 2009.

Subsequent meetings between DPAP and OSE to discuss further the appropriate risk management approach for Kalbitor resulted in a decision to retract the initial REMS notification letter and limit the REMS to a MG and CP only. DPAP and OSE determined a restricted program with ETASU was not necessary to ensure the benefits of the drug outweigh the risks of anaphylaxis at this time. The risk of hypersensitivity reactions is not unique to Kalbitor (ecallantide) and is an expected adverse event for a foreign protein-derived biologic product. Other drug products with a similar risk of anaphylaxis have not exhibited the need for a restricted program with elements to assure safe use, and there is no evidence to suggest that the nature of hypersensitivity reactions associated with Kalbitor (ecallantide) differs from more well-known drug-induced hypersensitivity reactions. Given the orphan status of the disease indication, it is anticipated that most HAE patients are under the care of specialists who are trained in allergy and immunology, and patients tend to seek emergency treatment from the same specialized centers, which may alleviate some of the potential confusion.¹

Therefore, ETASU as part of the REMS was not necessary at this time. However, because of the risk of anaphylaxis and overlapping symptoms with an acute HAE attack, additional measures to communicate this important information to patients and providers was considered necessary to ensure that the benefits of the drug outweigh the risks. Thus, the elements of the REMS were revised to include a Medication Guide, a communication plan, and a timetable for assessments. An Information Request (IR) letter reflecting this decision was sent October 16, 2009. The letter stated that the communication plan must include at a minimum the following:

- A Dear Healthcare Provider Letter to be distributed at the time of first marketing. Your communication plan should state specifically the types and specialties of health care providers to which the letters will be directed. These providers should include non-prescribers in specialties likely to treat HAE patients, such as emergency room providers.
- Dissemination of information about the need for distinguishing between hypersensitivity reactions and lack of product efficacy (persistent HAE symptoms).
- A schedule for when and how these letters/materials are to be distributed at the time Kalbitor (ecallantide) is approved, and at specified intervals thereafter, if this application is approved.

Interim Reviews by DRISK were forwarded to the review division on November 10, 2009 and November 17, 2009 addressing the DHCP letter, webpage, survey instruments and initial edits to the sponsor's November 16 REMS submission. This review pertains to the sponsor's submission from December 1, 2009, which is the final submission.

Comments related to the Kalbitor Medication Guide have been addressed in a separate review by the Patient Labeling reviewer.

¹Kalbitor REMS retraction memo, stamped October 16, 2009.

3 MATERIAL REVIEWED

- Risk Evaluation and Mitigation Strategy (REMS) submitted by the sponsor:
 - October 26, 2009 (response to IR letter)
 - November 16, 2009 submission (response to comments in OSE Interim Review #1 of November 10, 2009)
 - November 23, 2009 submission (response to comments in OSE Interim Review #2 of November 17, 2009)
 - November 27, 2009 submission
 - December 1, 2009 submission (response to request for addition of “see attached webpage” clause)
- Materials related to the February 4, 2009 Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting
 - FDA Briefing Package
 - Minutes
- Complete Response Letter, dated March 25, 2009
- REMS Information Request “Retraction” Letter, dated October 16, 2009

4 SPONSORS PROPOSED REMS

4.1 GOALS

The sponsor proposes the following goals:

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 educate patients about the serious risks associated with Kalbitor therapy.

4.2 REMS ELEMENTS

The proposed REMS includes a Medication Guide, communication plan, and a timetable for submission for assessments. The information needed for assessment of the REMS is included in REMS Supporting Document. Each element is described below and the final REMS is presented in Appendix A.

4.2.1 Medication Guide

DRISK’s review of the proposed Medication Guide will be provided separately.

A Medication Guide is enclosed within each Kalbitor carton (unit of use - containing three 10mg/mL vials) at the time of final product assembly along with the Full Prescribing Information. The carton prominently states “ATTENTION: Dispense the enclosed Medication Guide to each patient.” As the Medication Guide is included as part of the secondary package for Kalbitor, the requirement of 21 CFR 208.24 for distribution and dispensing of the Medication Guide are met.

4.2.2 Communication Plan

The sponsor will implement a communication plan 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. The initial audience for this CP includes healthcare providers (HCP) in the specialties of allergy/immunology and emergency medicine. Communication Plan materials include the Dear Healthcare Professional (DHCP) Letter as well as the Full Prescribing Information and the Medication Guide. These materials will be sent by direct mail.

The sponsor will issue the communication plan materials to healthcare providers at the time of product launch and yearly for 2 years thereafter. Additionally, for 2 years after launch, any known new prescribers of Kalbitor not previously targeted will be sent the DHCP letter.

The materials will also be provided by sales representatives during the first discussion of Kalbitor with potential prescribers during the first year of product availability. Additionally, the materials will be available through the www.kalbitor.com website through a stand-alone webpage.

The Dear Healthcare Professional Letter is attached in Appendix B.

The REMS webpage is attached in Appendix C.

4.2.3 Elements to Assure Safe Use

The REMS does not include any Elements to Assure Safe Use.

4.2.4 Implementation System

An implementation system is not a required component of the proposed REMS since there are no elements to assure safe use.

4.2.5 Timetable for Submission of Assessments

The Sponsor proposes the following timetable for submission of assessments of the Kalbitor REMS: 18 months, 3 years and 7 years after approval. The reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment time interval.

4.3 REMS Assessment Plan

Information needed for assessment is not a required element of the REMS Proposal. However, the sponsor provides the following information in the REMS Supporting Document.

- A. A summary of all reported serious hypersensitivity reactions with analysis of adverse event reporting by prescriber type.
- B. An evaluation of healthcare providers' understanding and patients' understanding of the serious risks of Kalbitor.

- C. A survey to evaluate HCP and patients' understanding of the risks of KALBITOR. The full survey methodology will be submitted to the FDA at least 90 days before the assessments will be conducted.
- D. Specification of measures that would be taken to increase awareness if surveys of HCPs indicate that provider awareness is not adequate.
- E. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- F. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
- G. Based on the information submitted, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

5 DISCUSSION

The sponsor's proposed REMS addresses the minimum requirements stipulated by FDA in the October 16, 2009 letter. The letter outlines two communication pieces – a DHCP letter and “dissemination of information about the need for distinguishing between hypersensitivity reactions and lack of product efficacy (persistent HAE symptoms).” The sponsor proposed only a DHCP letter which addresses both the risk of anaphylaxis and possible misdiagnosis of ongoing HAE attack vs anaphylaxis. Upon consultation with DPAP, they found it acceptable to have a DHCP letter and no other additional pieces. Also, the sponsor plans to provide access to Kalbitor REMS materials through a stand-alone webpage, which DRISK has found acceptable.

The Approval Letter cleared by OCC on December 1, 2009 specifically states:

The REMS assessment plan should include but is not limited to the following:

- a. A summary of all reported serious hypersensitivity reactions with analysis of adverse event reporting by prescriber type.
- b. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that provider awareness is not adequate.
- c. An evaluation of healthcare providers' understanding and patients' understanding of the serious risks of Kalbitor (ecallantide) injection.
- d. Based on the information submitted, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

Some elements were removed from the sponsor's proposal because they did not apply: periodic assessment related to the Medication Guides is not needed and issues related to distribution and dispensing do not apply since Kalbitor is unit of use. Information related to survey methodology was also removed from the REMS assessment section of the approval letter. Survey methodology is to be submitted at least 90 days before surveys would be conducted. It is DRISK's understanding that DPAP will work with the sponsor to meet this timeframe.

While not required to restrict distribution through the REMS, the Sponsor plans to use a single specialty pharmacy to distribute ecallantide. The specialty pharmacy will track all physicians and hospitals that order the drug. Also, DRISK acknowledges that additional data will be submitted through required post-marketing requirements the review division has outlined; planned studies will address anaphylaxis and identification of risk factors as well as immunogenicity issues. Information from future safety data may impact the scope and focus of the REMS for Kalbitor.

6 CONCLUSION AND RECOMMENDATIONS

The Division of Risk Management and the OSE Kalbitor Review team find the proposed REMS for Kalbitor (ecallantide) to be acceptable. The REMS materials applicable for this review include the REMS document (Appendix A), the DHCP Letter (Appendix B), and REMS webpage (link from the product website; Appendix C). OSE recommends approval of the Kalbitor REMS as submitted on December 1, 2009 with the comments below.

We have the following comments for the sponsor:

The FDA accepts the Kalbitor REMS as submitted in the December 1, 2009 submission.

- Please ensure that all communication materials accurately reflect the most recent language used in labeling.
- The full survey methodology should be submitted to the FDA at least 90 days before the surveys will be conducted.

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation (ODE) II
Division of Pulmonary and Allergy Products (DPAP)

NDA/BLA #s: BLA 125277
Product: Kalbitor (ecallantide) 30 mg SC injection

SPONSOR: Dyax Corp.
FROM: Sally Seymour, MD
Deputy Director for Safety, DPAP
DATE: September 29, 2009

OCT 16 2009

The purpose of this memorandum is to document the rationale for changing the elements of the proposed REMS for Kalbitor (ecallantide) compared to the elements that were required of Dyax in the Complete Response letter dated March 25, 2009. Kalbitor is a kallikrein antagonist proposed for a novel orphan indication, the treatment of acute attacks of hereditary angioedema (HAE).

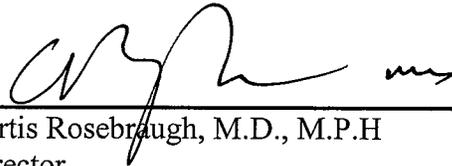
In a March 25, 2009, memorandum, FDA determined Kalbitor (ecallantide) was required to have a REMS to mitigate the risk of anaphylaxis with the following elements: a Medication Guide, a communication plan, elements to assure safe use, an implementation system, and a timetable for assessments of the REMS. The listed elements to assure safe use included a patient registry and monitoring, registration of prescribers and pharmacists, and documentation of safe-use conditions. In a Complete Response submission dated June 1, 2009, Dyax proposed a REMS including all of the components stipulated in the March 25, 2009 Complete Response letter. After further internal evaluation and discussion, DPAP and the Office of Surveillance and Epidemiology (OSE) have made the determination that the elements to assure safe use and implementation system are not needed at this time.

Although we believe a REMS is necessary to ensure the safe use of Kalbitor (ecallantide), DPAP and OSE do not believe that a restricted program with elements to assure safe use is necessary to ensure the benefits of the drug outweigh the risks of anaphylaxis. The risk of hypersensitivity reactions is not unique to Kalbitor (ecallantide) and is an expected adverse event for a foreign protein-derived biologic product. Other drug products with a similar risk of anaphylaxis have not exhibited the need for a restricted program with elements to assure safe use, and there is no evidence to suggest that the nature of hypersensitivity reactions associated with Kalbitor (ecallantide) differs from more well-known drug-induced hypersensitivity reactions. There remains some concern that the clinical signs and symptoms of HAE may overlap with the signs of drug hypersensitivity and cause confusion for healthcare providers and patients. For this reason, if Kalbitor (ecallantide) is approved, the FDA-approved labeling for Kalbitor (ecallantide) will recommend that the drug be administered in a setting that is equipped to

manage anaphylaxis. Given the orphan status of the disease indication, we anticipate most HAE patients are under the care of specialists who are trained in allergy and immunology, and patients tend to seek emergency treatment from the same specialized centers, which may alleviate some of the potential confusion.

In addition, we have determined that we cannot conclude that the proposed elements to assure safe use would mitigate the risk of anaphylaxis, and they could hinder patient access. Specifically, the proposed elements to assure safe use could interfere with the availability of Kalbitor (ecallantide) and increase the risks of a delay in treatment. Because acute attacks of HAE are potentially serious and life threatening, a delay or limitation in access is not desirable.

Therefore, although we continue to believe that a REMS is necessary to ensure the benefits of Kalbitor (ecallantide) outweigh its risks, we have concluded that it is not necessary to include elements to assure safe use as part of the REMS. However, the unique characteristic of the risk – anaphylaxis – that may overlap with presenting symptoms of the disease, does support communicating this important information to patients and providers. Thus, the elements of the REMS will be a Medication Guide, a communication plan, and a timetable for assessments.



Curtis Rosebraugh, M.D., M.P.H
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Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Division of Pulmonary and Allergy Product**

MAR 25 2009

NDA/BLA #s: BLA# 125277
Products: KALBITOR, ecallantide, solution for injection
SPONSOR: Dyax Corp.
FROM: Curtis J. Rosebraugh, MD, MPH
Director, Office of Drug Evaluation II

[Handwritten signature] 3/25/09

DATE: March 25, 2009

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). 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 (NME).

During review of the BLA for Kalbitor (ecallantide) for treatment of acute attacks of hereditary angioedema, anaphylaxis was identified as a safety signal. After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes [REDACTED] (b) (4) Kalbitor (ecallantide) to ensure that the benefits of the drug outweigh the risks of anaphylaxis. In reaching this determination, we considered the following:

- A. Hereditary angioedema (HAE) is a rare, autosomal dominant disorder that affects approximately 1 in 10,000 to 1 in 150,000 individuals. This estimate is based upon general estimates of prevalence in the literature¹. Because of the rarity of HAE, the Kalbitor (ecallantide) program has been granted orphan drug status.
- B. Hereditary angioedema is a rare, autosomal dominant disorder that is characterized by intermittent, unpredictable attacks of subcutaneous or submucosal edema of the face,

¹ Nzeako UC et al. Arch Intern Med 2001; 161 (2417-2429).

larynx, gastrointestinal tract, limbs, and/or genitalia. Attacks can be life-threatening, particularly those attacks involving the airway. Attacks can also lead to significant morbidity, including hospitalization or even surgery for abdominal pain.

- C. Currently, no products are approved for the treatment of acute attacks in the United States. Therefore, there is an unmet need in the HAE community for a product to treat acute attacks. In two placebo controlled clinical trials, compared to placebo, Kalbitor (ecallantide) improved symptoms in patients with acute attacks of HAE.
- D. If approved, Kalbitor (ecallantide) would be expected to be used widely in the HAE population, as there is currently no drug approved for the treatment of acute attacks of HAE. Since HAE attacks are unpredictable and occur intermittently, Kalbitor (ecallantide) has the potential for chronic intermittent use. It is possible that some patients could use Kalbitor (ecallantide) on an intermittent basis for their lifetime.
- E. Kalbitor (ecallantide) is a therapeutic protein and is immunogenic, which predisposes to hypersensitivity reactions. Anaphylaxis was noted as a safety signal in the clinical program submitted to support the efficacy and safety of Kalbitor (ecallantide). Anaphylaxis is a severe, potentially fatal, systemic allergic reaction. Using diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis², 9 potential cases of anaphylaxis were identified out of 243 HAE patients treated with Kalbitor (ecallantide), for an anaphylaxis rate of 3.7%. Most of these reactions occurred following repeat dosing of Kalbitor (ecallantide).

Regarding a background rate of anaphylaxis in this population, anaphylaxis is an event that occurs following contact with an allergy-causing substance. Patients would not normally have anaphylaxis as an event unless coming into contact with an allergen. Many of the HAE symptoms are similar to anaphylaxis, which could make it difficult to determine if an anaphylaxis event occurs. The rate of anaphylaxis in the ecallantide clinical program may be an underestimate because of the overlapping of symptoms of HAE attacks and anaphylaxis.

- F. Kalbitor (ecallantide) is a new molecular entity.

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. Pursuant to 21 CFR Part 208, FDA has determined that Kalbitor (ecallantide) 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 Kalbitor (ecallantide). FDA has determined that ecallantide is a product that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use Kalbitor (ecallantide).

² Sampson HA et al. J Allergy Clin Immunol 2006; 117:391-7.

The elements of the REMS will be a Medication Guide, communication plan, (b) (4)
(b) (4)

pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified under 505-1(f)(3)(B); patients are dispensed the drug under safe use conditions under 505-1(f)(3)(D); (b) (4)

(b) (4), an implementation system, and a timetable for submission of assessments of the REMS.