

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125277

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	December 1, 2009
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA #	N 125277
Supp #	
Applicant Name	Dyax Corporation
Proprietary / Established (USAN) Names	Kalbitor ecallantide
Dosage Forms / Strength	Solution 10 mg/mL
Proposed Indication(s)	Treatment of acute attacks of hereditary angioedema (HAE)
Action:	<i>Approval</i>

1. Introduction and Discussion

This review will be a brief summary of the second review cycle and basis for the regulatory action regarding ecallantide. The reader should refer to the reviews in the action package and my previous review for a more detailed discussion. The reader should also refer to Drs. Seymour and Chowdhury's reviews, with which I am in full agreement.

As noted by Dr. Seymour, Dyax submitted the original BLA on September 23, 2008 and received a Complete Response (CR) action on March 25, 2009. This action was taken because, although ecallantide had demonstrated efficacy for the population evaluated, the sponsor had requested a claim including patients 10 years of age and greater without having sufficient supporting data for pediatric patients. Additionally, we determined that a Risk Evaluation Mitigation Strategy (REMS) would be necessary to mitigate the risk of anaphylaxis associated with use of this product. As well as these two issues, the application also had numerous product quality deficiencies. This submission has adequately addressed all of these deficiencies in that the requested indication now advocates use for ages 16 years and above (age groups supported by data), the sponsor has submitted an adequate REMS and all the product quality issues have been addressed. Therefore, this application should be approved.

Regarding the age for indication, we originally had suggested that the data only supported use in age greater than 18 years of age, but the sponsor was able to include enough data and a validated pharmacokinetic study to support lowering the dosage range to 16 years of age.

The original REMS request from us required components which included a Medication Guide, Communication Plan, and Elements to Assure Safe Use (ETASU) which would have restricted distribution. In discussion with the Office of Surveillance and Epidemiology (OSE) and the Division of Risk Management (DRISK), it was decided that ETASU were not appropriate for this product. This decision was made because we determined that a restricted distribution

program would not mitigate the risk of anaphylaxis as these reactions cannot be anticipated or prevented and the nature of hypersensitivity did not seem to differ from other drugs with anaphylaxis which do not currently have restricted distribution programs. We also felt that a restricted distribution program may actually hinder patient access in an unacceptable manner. Also, an important factor in our decision and decreasing our concern is that HAE patients are a limited population that for the most part is under the care of specialists in specialized centers trained in allergy and immunology who are equipped to manage both hereditary angioedema attacks and anaphylaxis. During our discussion it became apparent that our original REMS request would not actually mitigate the risk of anaphylaxis as there was not any way to predict who may have such a reaction and the feasibility of implementation of this complex REMS was questionable and may actually hinder patient access. After multiple discussions, we concluded that a REMS was necessary, but concluded that it should consist of a Communication Plan and Medication Guide with a timetable for assessments to assure safe use. We also felt that if future assessments that will be required under the REMS demonstrate that this program needs modification, we have the authority to modify the REMS in the future.

Conclusions and Recommendations

I am in full agreement with the reviews of Drs. Seymour and Chowdhury. As I had said in my first review, HAE can be a devastating and life-threatening disease as was clearly described by the numerous patients that presented the challenges of their lives during the open public session at the Advisory Committee meeting. Frustrating their lives is that until very recently, we did not have an approved therapy for the treatment of acute attacks. Recently, however, a human plasma-derived C1 esterase inhibitor (Berinert) was approved for the treatment of acute abdominal or facial attacks of HAE in adult and adolescent patients.

Ecallantide allows the promise of another therapy, but should be used with the knowledge that it has the potential to cause hypersensitivity/anaphylaxis reactions. The sponsor has addressed our concerns from the first cycle of the application that led to a CR action and as such I recommend Approval.