

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125277

OTHER 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: November 20, 2009

To: Badrul Chowdhury, MD, Director
Division of Pulmonary and Allergy Products (DPAP)

Through: Claudia Karwoski, PharmD, Director *Claudia Karwoski*
Division of Risk Management (DRISK)

LaShawn Griffiths, MSHS-PH, BSN, RN *LaShawn Griffiths*
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Sharon R. Mills, BSN, RN, CCRP *Sharon R. Mills 11/20/2009*
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide),

Drug Name(s): KALBITOR (ecallantide)

Application Type/Number: BLA 125277

Submission Receipt Date: May 31, 2009

Applicant/sponsor: Dyax

OSE RCM #: 2009-103

1 INTRODUCTION

On May 31, 2009 Dyax submitted a complete response to the Agency Complete Response action letter dated March 25, 2009 for BLA 125277 for KALBITOR (ecallantide). KALBITOR (ecallantide) is indicated for treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older.

This review is written in response to a request by the Division of Pulmonary and Allergy Products (DPAP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for KALBITOR (ecallantide). Please let us know if DPAP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. The proposed REMS is being reviewed by DRISK and will be provided to DPAP under separate cover.

2 MATERIAL REVIEWED

- Draft KALBITOR (ecallantide) Prescribing Information (PI) submitted May 31, 2009 and revised by the Review Division throughout the current review cycle; most recent FDA version dated November 5, 2009 and most recent Applicant submission dated November 11, 2009.
- Draft KALBITOR (ecallantide) Medication Guide (MG) submitted on May 31, 2009, further revised and submitted on November 11, 2009.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- rearranged information due to PLR format
- removed unnecessary or redundant information
- ensured that the MG 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)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

11 PP WITHHELD IMMEDIATELY AFTER THIS PAGE AS DRAFT LABELING (B)(4).



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 19, 2009

To: Badrul Chowdhury, M.D., Ph. D., Director
Division of Pulmonary and Allergy Products

Through: Jodi Duckhorn, MA, Team Leader *Jodi Duckhorn 2/19/2009*
Patient Labeling and Education Team
Division of Risk Management

From: Nancy Carothers, RN, BA *Nancy Carothers 2/19/2009*
Patient Product Information Reviewer
Patient Labeling and Education Team
Division of Risk Management

Subject: Memo to File Regarding Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Kalbitor (ecallantide) Subcutaneous Injection

Application Type/Number: BLA STN 125277

Applicant/sponsor: Dyax Corp

OSE RCM #: 2009-87

Dyax Corp. submitted an original application, BLA STN 125277, for Kalbitor (ecallantide) Subcutaneous Injection on September 23, 2008. Kalbitor is a plasma kallikrein inhibitor indicated for the treatment of acute attacks of hereditary angiodema (HAE).

The Division of Pulmonary and Allergy Products (DPAP) requested that the Division of Risk Management's Patient Labeling and Education Team review the sponsor's proposed Kalbitor Patient Package Insert which was submitted with the Package Insert. Following the recent Advisory Committee meeting on February 4, 2009, DPAP decided that Kalbitor (ecallantide) will receive a Complete Response in March 2009.

The Patient Labeling and Education Team does not plan to complete this review until such time that DPAP plans to address labeling. If at some point in the future the Kalbitor Patient Package Insert is resubmitted, please send a new consult for the Kalbitor review.

This memo serves to close-out the consult request for Kalbitor (ecallantide).

Please let us know if you have any questions.

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

Memorandum

Date: November 3, 2009

To: Colette Jackson -- Regulatory Project Manager
Division of Pulmonary and Allergy Products (DPAP)

From: Robyn Tyler, Regulatory Review Officer *Robyn Tyler*
Samuel M. Skariah, Regulatory Review Officer *Samuel Skariah*
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: BLA #125277
DDMAC labeling comments for KALBITOR (ecallantide) for
subcutaneous injection

DDMAC has reviewed the proposed product labeling (PI) and Medication for KALBITOR (ecallantide) for subcutaneous injection (Kalbitor) submitted for consult on June 5, 2009.

DDMAC offers the following comments.

Full PI

4 CONTRAINDICATIONS

[REDACTED] (b) (4)

Is KALBITOR only contraindicated in patients with a [REDACTED] (b) (4) of clinical hypersensitivity? If not, please consider deleting the term [REDACTED] (b) (4) from the full PI and the Highlight sections.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Including Anaphylaxis

[REDACTED] (b) (4)

Please see comment above.

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

Memorandum

Date: January 15, 2009

To: Colette Jackson—Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

From: Jessica Adams—Regulatory Review Officer *JA*
Shefali Doshi—Consumer Safety Officer *SSD*
Division of Drug Marketing, Advertising and Communications

Subject: DDMAC labeling comments
BLA 125277 KALBITOR (ecallantide) Injection for subcutaneous
use

DDMAC has reviewed the proposed product labeling (PI), proposed carton and container labeling, and proposed PPI for KALBITOR (ecallantide) Injection for subcutaneous use submitted for consult on October 9, 2008.

DDMAC does not have any comments at this time on the proposed carton and container labeling.

The following comments are provided using the updated version of the proposed PI, dated December 17, 2008.

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SEALD LABELING REVIEW

| | |
|--------------------|---------------------------|
| APPLICATION NUMBER | BLA 125277 |
| APPLICANT | Dyax, Corporation |
| DRUG NAME | KALBITOR (ecallantide) |
| SUBMISSION DATE | January 2, 2009 |
| SEALD REVIEW DATE | November 25, 2009 |
| SEALD REVIEWER(S) | Jeanne M. Delasko, RN, MS |

Jeanne M. Delasko

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

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: STN 125277/0

Name of Drug: Kalbitor®

Sponsor: Novartis Pharmaceutical Corporation

Material Reviewed: Kalbitor® (ecallantide) Carton and Container Labels

OBP Receipt Date: February 3, 2009

Original Review Date: July 20, 2009

Amendment Reviewed: August 12, 2009, November 4, 2009

EXECUTIVE SUMMARY

The carton and container labels for Kalbitor® (ecallantide) were reviewed and found to comply with the following regulations : 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57 and 21 CFR 200.100. Labeling deficiencies were identified, addressed and mitigated. An overfill issue was also identified and mitigated. Please see comments in the conclusions section.

Background

STN 125277/0 for ecallantide is an original Biologic License Application (BLA) indicated for the treatment of acute attacks of hereditary angioedema (HAE). The product is supplied as a clear and colorless, sterile, and nonpyrogenic solution in 10 mg/mL single use vial. A single dose consists of 30 mg or three 1 mL vials injected subcutaneously.

Labels Reviewed:

Kalbitor® (ecallantide) Container Label

Vial label
Kalbitor[®] (ecallantide) Carton Label
Outside Carton label
Inside Carton label
Kalbitor[®] (ecallantide) Package Insert Label

Submission 31 MAY 2009

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Conclusions

The following deficiencies and recommendations were noted in the initial review of the ecallantide container and carton labels and revised labels were found acceptable:

1. Please indicate how the label is affixed to the vial and where the visual area of inspection is located as per 21 CFR 610.60 (e). Information provided and acceptable.
2. Please relocate the license number to the following presentation per 610.61(b).
Dyax Corp.
300 Technology Square
Cambridge, MA 02139
License: XXXX
Change made and acceptable.
3. Please add the statement "Do Not Freeze" capitalized and in bold type per 21 CFR 610.61(i) on all labeling. Change made and acceptable on carton label. The Justification for container label is acceptable.
4. Please consider relocating the NDC number to the top third of the primary display panel of the carton for improved readability and consistency with other prescription products. Change made and acceptable.
5. Please add the statement "No U.S. standard of potency" to the carton label to comply with 21 CFR 610.61(r). Change made and acceptable.
6. Please add the statement, "Dispense the enclosed Medication Guide to each patient" to the carton per 21 CFR 610.60. Change made and acceptable.
8. Please provide font size configurations for all carton and container labels. Information provided and acceptable.

Package Insert comments

- Per USPC Official 8/1/09-12/1/09, USP 32/NF27, <1091> Labeling of Inactive Ingredients, please list the names of all inactive ingredients in alphabetical order in the "DESCRIPTION" section. Change made and acceptable.
- Per 21 CFR 201.57(12)(D), please indicate that the ecallantide is a sterile product in the "DESCRIPTION" section. Change made and acceptable.

Revised Labels submitted 12 AUG 2009



(b) (4)



(b) (4)

The following deficiencies were noted in the revised submission of the ecallantide container and carton labels:

1. Please separate and relocate the dosage form and route of administration on the primary panel. Consider the following presentation:
Kalbitor
(ecallantide)
Injection
For Subcutaneous Use
***Strength Defer to CMC and DMEPA final determination

Change made and acceptable.

Presentation changed to:

Kalbitor

Ecallantide

10 mg/mL

Injection

For Subcutaneous Use Only

2. Please add applicable agents or a reference to applicable agents to carton labels to comply with 21 CFR 610.61(l)(m)(o)(p)(q). The statement, "See package Insert for Ingredient Information" was added to the carton. Addition acceptable. This conforms to the regulation.
3. Additional changes noted on the update labels include:
 - a. Containe (b) (4) was replaced by "Single Use; -
-Discard Unused Portion".
-The logo with a blue circled K was also removed.
 - b. Carton: The NDC number was moved from the primary panel to the back panel area above the barcode. A net quantity statement was added. "Net Quantity: 3 Vials". The prominence of the primary strength was changed from (b) (4)" to "10 mg/mL".

Revised labels submitted 26 OCT 2009

Container Label



(b) (4)

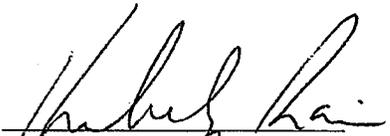
The product contains an overfill of (b); mL per vial. Consultation with Yana Mille and Richard Lostritto from the Nomenclature and Labeling Committee yielded the following recommendations.

1. The DMEPA recommendation to label the ecallantide product with a concentration of (b) (4). We do not concur. Rationale: The target concentration (10 mg/mL) should be labeled and the overfill should be addressed from a manufacturing perspective. The product labeled with the target concentration of 10 mg/mL and the dose with three 1 mL injections is appropriate for practitioners to use correctly. In addition, if the drug is labeled with the overfill amount as (b);mL the applicant will have to increase the amount of product in each vial to allow the withdrawal of the labeled amount of (b) mL to meet the regulations. Consequently, the vial will contain an additional overfill and cause a greater chance for overflow per (21 CFR 201.51(g)).
2. The DMEPA alternative 10 mg/mL * each vial contains (b) (4)mL of Kalbitor- We do not concur. This presentation does not meet the regulations and labels the overfill. We feel this presentation will cause additional confusion and conflicts with the regulations. In addition, this is a precedence that may lead to mislabeling products to mitigate erroneous dispensing and/or administration practices performed by frontline practitioners.
3. We recommend that the product be labeled with the target concentration of 10 mg/mL and that an explanation is provided on the carton away from the proximity of the primary strength to indicate that there is an excess of (b) mL of Kalbitor included in each vial to allow for the delivery of each 1 mL dose. In addition, a similar or same explanation should be in the Package Insert under Dosage and Administration and where applicable.

4. Final agreement: The strength presentation, 10 mg/mL with the statement "Each vial contains a slight overfill". Steven Kozlowski, Director, Office of Biotechnology Products concurs with this presentation.

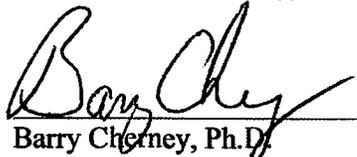
5. We also believe that a PMC is necessary to address the root of this issue-packaging. The following PMC was provided to the sponsor:

To evaluate the minimal fill volume required for appropriate dosage withdrawal and to adjust the final fill volume for the drug product to reduce the likelihood that a patient could be overdosed with the excess drug product. The final study report and new fill volume, if necessary will be submitted in a supplement to the license by XXXXX.

 11/20/09
Kimberly Rains, Pharm.D
Regulatory Project Manager
CDER/OPS/OBS

Comment/Concurrence:

 11/20/09
Kathy Lee, M.S.
Product Reviewer
Division of Therapeutic Proteins
CDER/OPS/OBP

11/20/09

Barry Cherney, Ph.D.
Deputy Director
Division of Therapeutic Proteins
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