CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-386

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:	May 23, 2008
To:	Mary Parks, M.D. Director, Division of Metabolism and Endocrinology Products
Through:	Carol Holquist, RPh, Director Division of Medication Error Prevention
From:	Todd Bridges, RPh, Team Leader Division of Medication Error Prevention
Subject:	Label and Labeling Review for PrandiMet
Drug Name(s):	PrandiMet (Repaglinide and Metformin HCl Tablets)
Application Type/Number:	NDA #22-232
Submission Number:	Not applicable
Applicant:	Novo Nordisk
OSE RCM #:	2008-795

We would be willing to meet with the Division for further discussion, if needed. DMETS would appreciate feedback of the final outcome of this consult. Please copy DMETS on any communication to the sponsor with regard to this review. If you have further questions, or need clarifications, please contact Cheryl Campbell, OSE project manager, at 301-796-0723.

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Other Review(s) - 1

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/s/

Todd Bridges
5/28/2008 09:38:45 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/28/2008 09:53:35 AM
DRUG SAFETY OFFICE REVIEWER

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 16, 2007
To:	Mary Parks, M.D. Director, Division of Metabolism and Endocrinology Products
Thru:	Todd Bridges, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Errors and Technical Support
From:	Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator Division of Medication Errors and Technical Support
Subject:	Medication Error Labels and Labeling Review for PrandiMet
Drug Name(s):	PrandiMet (Repaglinide/Metformin HCl tablets) 1 mg/500 mg, 2 mg/500 mg
Application Type/Number:	NDA #22-232
Submission Number:	Not applicable
Applicant/sponsor:	Novo Nordisk Inc.
OSE RCM #:	2007-1946

1 INTRODUCTION

This memorandum is in response to a September 11, 2007, request from the Division of Metabolism and Endocrinology Products for a review of the container labels, carton and insert labeling of PrandiMet. The request for assessment of the proprietary name, PrandiMet, was submitted separately to OSE and will be forthcoming in a separate review (OSE RCM #2007-1326).

2 MATERIALS REVIEWED

Container labels, carton and insert labeling submitted on August 15, 2007.

3 DISCUSSION

In reviewing the labels and labeling, we noted the color of the two different strengths is identical; [redacted] This similarity raises concern that the 1 mg/500 mg and 2 mg/500 mg strengths could be confused, leading to selection errors and potentially resulting in the dispensing and/or administration of the wrong strength. [redacted] b(4)

the two colors used are very similar hues and thus do not provide sufficient differentiation. Additionally, the sponsor has presented the first number of the strengths in larger font (i.e., *2* mg/500 mg and *1* mg/500 mg) to differentiate the strengths. However, this difference is so insignificant that it is not likely to be noticed by dispensing practitioners. Based on postmarketing experience, labels that utilize identical trade dress and are not adequately differentiated contribute to product mix-ups and medication errors resulting in overdose or underdose because the wrong strength was dispensed and administered. The color differentiation would be more effective if it also appeared around the strength. [redacted] b(4)

Furthermore, the strength and net quantity are in close proximity to one another. We have learned from postmarketing reporting that confusion can occur between the net quantity and product strength if they are presented in close proximity to one another. Therefore, these areas of the labels should be revised to reduce the risk of selection errors.

[redacted]

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b(4)

4 CONCLUSION AND RECOMMENDATIONS

The similarity of the labels and labeling between the strengths is a potential source of product selection errors. DMETS has the following label and labeling recommendations in the interest of decreasing the potential for user error with PrandiMet.

4.1 GENERAL COMMENTS

4.1.1 Ensure the established name is at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2).

4.1.2 "Met" in PrandiMet is italicized. Revise so that the entire proprietary name is presented in the same type, color, and size font. Additionally, the letter "m" should not be capitalized because it overemphasizes the second portion of the name.

4.1.3 In order to provide additional differentiation of the strengths, remove the colored box from the trade and established names and place it around the product strength. In addition, provide more color differentiation between the 2 strengths as these colors appear similar when placed side by side.

4.1.4 Revise the strength so that both number components appear the same size, by increasing the size of the 500 mg portion to be the same size as the 1 mg and 2 mg portion (e.g. the 1 mg and the 500 mg should be presented in the same font size, type and color.)

4.1.5 ⌜

⌟ b(4)

4.1.6 Relocate the net quantity away from the strength, ensure it is not bolded and is less prominent than the strength.

4.1.7 DMETS questions why PrandiMet is available in a net quantity of 20 tablets? According to the recommended dosage, PrandiMet should be given 2-3 times a day with meals; however, this package size does not support the usual dosage that would require 60 to 90 tablets. Please explain the rationale for this package size.

4.1.8 Revise the word "control" number to read "lot" number as lot number is widely recognized by U.S. healthcare providers and patients.

4.2 CARTON LABELING

4.2.1 Add the dosage form "tablets" following the established name.

4.2.2 See General comments 4.1.1 through 4.1.8.

4.3 CONTAINER LABEL

4.3.1 See General comments 4.1.1 through 4.1.8.

4.4 INSERT LABELING

4.4.1 See General comments 4.1.2.

We would be willing to meet with the Division for further discussion, if needed. DMETS would appreciate feedback of the final outcome of this consult. Please copy DMETS on any communication to the sponsor with regard to this review. If you have further questions, or need clarifications, please contact Cheryl Campbell, OSE project manager, at 301-796-0723

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/s/

Deveonne Hamilton-Stokes
11/16/2007 02:38:27 PM
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11/16/2007 02:49:49 PM
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Denise Toyer
11/16/2007 02:51:41 PM
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11/16/2007 04:31:40 PM
DRUG SAFETY OFFICE REVIEWER

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Metabolism and Endocrinology Products

Application Number: 22-232

Name of Drug: Prandi*Met* (repaglinide and metformin fixed dose combination) Tablet

Applicant: Novo Nordisk Inc.

Material Reviewed:

Submission Date(s): August 15, 2007

Receipt Date(s): August 15, 2007

Submission Date of Structure Product Labeling (SPL): August 15, 2007

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

Recommendations

Please address the identified deficiencies/issues and re-submit labeling by October 19, 2007. This updated version of labeling will be used for further labeling discussions.

Highlights

Beginning of Highlights

- Remove "for oral use." following "Prandi*Met* (repaglinide and metformin HCl) Tablets". If the route of administration is typical for the dosage form and is commonly understood (e.g., tablets for oral use), the route of administration should be omitted.

Dosage Forms and Strengths

- Move the Dosage Forms and Strengths section of Highlights to the second column so that both columns are of approximately equal length. Highlights, excluding the boxed warning, must be limited in length to one-half page. The proposed Highlights seem to meet this requirement if the boxed warning is excluded.
- Remove the word "available".

Adverse Events

- Add the criteria used to determine inclusion in this section (e.g., incidence rate greater than x%).

Use in Specific Populations

- The absence of information should not be included under this heading in Highlights. Since Use in Specific Populations is an optional heading in Highlights, this section should be removed.

FPI: Contents

- Add "WARNING – LACTIC ACIDOSIS" in bold font above "1 INDICATIONS AND USAGE".
- The first letter of each major word in the subsection headings should be capitalized (e.g., "5.3 Assessment of Renal Function").

Boxed Warning

- "Prandi*Met*" appears to be in smaller font than the rest of the boxed warning.

Dosage and Administration

- Bulleting is not recommended in the Full Prescribing Information. We recommend using subheadings to organize the information.

Dosage Forms and Strengths

- Bulleting is not recommended in the Full Prescribing Information. We recommend using subheadings to organize the information.

Contraindications

- Each Contraindication should be identified with its own subheading.

Use in Specific Populations

- Under subheading 8.1 Pregnancy, the statement "Pregnancy Category C." should be moved to the beginning of the paragraph that starts with, "There are no adequate…"

Other

- Remove the header from each page

Reviewed by:
Julie Marchick, MPH
Regulatory Project Manager

Supervisory concurrence:
Lina AlJuburi, Pharm.D., M.S.
Chief, Project Management Staff

Drafted: JM/09.18.07
Finalized: JM/09.24.07

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/s/

Julie Marchick
9/26/2007 11:25:20 AM
CSO