CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-386

PHARMACOLOGY REVIEW(S)

Signed off in DFS on 5/20/08

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-232
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	8/15/2007
PRODUCT:	PrandiMet (fixed dose combination of repaglinide/metformin)
INTENDED CLINICAL POPULATION:	patients with type 2 diabetes
SPONSOR:	Novo Nordisk, Princeton, NJ.
DOCUMENTS REVIEWED:	e-CTD submission.
REVIEW DIVISION:	Division of Metabolsim and Endocrinoloogy Products (HFD-)
PHARM/TOX REVIEWER:	Indra Antonipillai
PHARM/TOX SUPERVISOR:	Karen Davis Bruno
DIVISION DIRECTOR:	Mary Parks
PROJECT MANAGER:	Julie Marchick

Date of review submission to Division File System (DFS): 5/20/2008

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Executive Summary

1. Recommendations

A. **Recommendation on approvability**
Pharmacology recommends approval of this drug for proposed indications

B. **Recommendation for Nonclinical Studies**:
The preclinical studies are not required for this drug product, since this drug product is a combination of two approved reference listed drugs repaglinide (NDA 20-741) and metformin HCl (DMF —— at two dosage strengths of 1/500 and 2/500 mg repaglinide/metformin HCl respectively. The toxicity studies have been conducted with these drugs under previous NDAs. b(4)

C. **Recommendation on Labeling**: The pharmacology toxicology labeling in general is similar to the approved repaglinide and metformin labels. In the current application, label has been provided in the PLR format, which is reviewed and recommended changes are stated (see the label on pages 9-14).

II. Summary of Nonclinical Findings:

A. Brief Review of Nonclinical studies
Repaglinide (or Prandin) is an approved drug for treatment of patients with diabetes melltus (NDA 20-741) Similarly Metformin is an approved drug (DMF —— No new non-clinical studies have been provided in the current submission since PrandiMet is a fixed dose combination of the above two drugs. This application is a 505 b(2) which relies on the previous studies of repaglinide and metformin. b(4)

B. Pharmacologic activity
Repaglinide (Prandin) is a short acting insulin seceretagogue indicated for the management of type 2 diabetes. Repaglinide is an inhibitor of potassium currents of ATP-sensitive potassium (K_{ATP}) channels found in the outer membrane of pancreatic beta cells. Closure of these potassium channels causes opening of voltage-dependent calcium channels, followed by calcium influx which triggers cellular insulin release. Thus, It lowers the blood glucose by stimulating the release of insulin from pancreas.

Metformin HCl (glucaphage) is an insulin sensitizer which improves both basal and postprandial plasma glucose in patients with type 2 diabetes. The principal action of metformin is to reduce hepatic glucose output, it decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

C. Nonclinical safety issues relevant to clinical use
There are no new non-clinical safety issues relevant to the clinical use with the current drug product.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: NDA 22-232
Review Number: 1

Sequence number/date/type of submission: 8/15/2007, 10/19/07 (original application). It is a 505(b)(2) application., it is an e-CTD submission.
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Information to sponsor: Yes ( ) No (X)

Sponsor: Novo Nordisk, Princeton, NJ.

Manufacturer for drug substance: Metformin is manufactured by [redacted] Repaglinide is manufactured at [redacted] The drug product (i.e. NN4440 tablet) is manufactured at [redacted] and packaging of the product is done in [redacted] b(4)

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.
Division: Division of Metabolism and Endocrinology Products (DMEP).
Review completion date: 5/5/08.

Drug:
Trade name: PrandiMet is a fixed dose combination of two approved drug products repaglinide and metformin HCL.

Code name: NN44440 is the code name for the combination product (repaglinide/metformin).

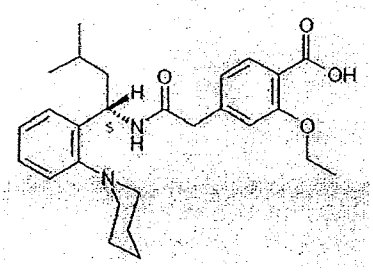
Chemical name: of Repaglinide (Prandin)
(S)-2-ethoxy-4-[2-[[methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoic acid
Chemical name of Metformin (Glucophage):
1,1-dimethylbiguanide hydrochloride

CAS registry number:
Repaglinide is 135062-01-1;
for Metformin is 1115-70-4
Mole file number: N/A

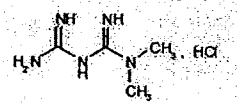
Molecular formula/molecular weight:
Repaglinide $C_{27}H_{36}N_2O_4$/452.61
Metformin HCl is $C_4H_{12}ClN_4$/165.6

Structures of repaglinide and metformin are shown below:

The Chemical Structure of Repaglinide



The Chemical Structure of Metformin HCl



Relevant INDs/NDAs/DMFs: NDA 20-741 (prandin, repaglinide, NovoNorm, glucoNorm.), DMF —— (metformin hydrochloride), DMF —— (for repaglinide), NDA 20-357 and NDA 21-202 (glucophage). IND 70,959 was submitted to our Division for repaglinide + metformin fixed dose combination on 4/13/2006. b(4)

Drug class: Repaglinide is an insulin secretagogue. Metformin is insulin sensitizer.

Indication: The fixed dose combination of these two drugs repaglinide/metformin is indicated for the treatment of patients with type 2 diabetes mellitus where treatment with both drugs (metformin and repaglinide) is appropriate. The fixed dose combination will be indicated for patients whose diabetes is not adequately controlled with either drug alone.

Clinical formulation: The drug product, fixed dose combination (FDC) tablets are formulated in the following dosage strengths 1/500, 2/500 mg of repaglinide /metformin. The two strengths of the drug product tablets are identical in size and shape (—— biconvex), but differ in color and coding. The lower strength (1/500) tablet is yellow, whereas, the higher strength (2/500) tablet is pink. b(4)

The combination tablet NN4440 is manufactured with repaglinide —— and metformin HCl [ ] b(4)

The formulation containing repaglinide/metformin HCL (1/500, 2/500 mg respectively) active drugs and inactive excipients is shown below.

Appears This Way
On Original

Table 1 Composition of Repaglinide 1 or 2 mg, Metformin HCl 500 mg tablet

Component	Amount per Tablet (mg) 1/500	Amount per Tablet (mg) 2/500	Function	Reference to Standards
Drug Product				
Repaglinide	1.00	2.00	Active ingredient	Ph. Eur./ USP
Poloxamer 188				Ph. Eur./ NF
Povidone				Ph. Eur./ USP
Meglumine				Ph. Eur./ USP
				Ph. Eur./ USP
Cellulose, Microcrystalline				Ph. Eur./ NF[2]
Metformin Hydrochloride	500	500	Active ingredient	Ph. Eur./ USP
Povidone				Ph. Eur./ USP
				Ph. Eur./ USP
Sorbitol				Ph. Eur./ NF
Macrogol				Ph. Eur./ NF[3]
Excipients				
Cellulose, Microcrystalline				Ph. Eur./ NF[2]
Polacrilin Potassium				NF
Magnesium Stearate				Ph. Eur./ NF
Hypromellose 6cP				Ph. Eur./USP
Talc				Ph. Eur./USP
Titanium Dioxide				Ph. Eur./USP
Macrogol				Ph. Eur. /NF[4]
Iron Oxide Yellow				NF[5]
				Ph. Eur./USP
Hypromellose 3cP				Ph. Eur./ USP
Talc				Ph. Eur./ USP
Titanium Dioxide				Ph. Eur./ USP
Propylene Glycol				Ph. Eur./ USP
Iron Oxide Red				NF[5]
Hypromellose 6cP				Ph. Eur./ USP
Titanium Dioxide				Ph. Eur./ USP
Macrogol				Ph. Eur./NF[4]
				Ph. Eur./ USP

1.
2. Microcrystalline Cellulose NF
3. Polyethylene Glycol
4. Polyethylene Glycol
5. Conforms to the monograph of Ferric Oxide, NF

b(4)

b(4)

Best Possible Copy

[

b(4)

]

Fixed dose combination (FDC) tablets contain the following excipients: polacrillin potassium, microcrystalline cellulose, magnesium stearate [

b(4)

] All excipients except [ ] are of pharmacopeia standard. All of these excipients are included in one or both of the currently marketed products (i.e.repaglinide and metformin tablets).

Route of administration: Oral.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise

Data reliance: This is 505(b)(2) application: Sponsor refers to two approved listed drug products that are the basis for the current submission. These are repaglinide (NDA 20-741) and metformin (DMF

b(4)

Studies reviewed within this submission: This is a 505(b)(2) application, which relies on the previous studies of repaglinide and metformin, which are combined here in a fixed dose formulation. In the current application, label has been provided in the PLR format, which is reviewed here.

Studies not reviewed within this submission: None

2.6.1 INTRODUCTION AND DRUG HISTORY

Repaglinide (Prandin) is a short acting insulin seceretagogue indicated for the management of type 2 diabetes. It lowers the blood glucose by stimulating the release of insulin from pancreas. This effect is dependent on functioning beta cells in the pancreatic islets. Repaglinide is an inhibitor of potassium currents of ATP-sensitive potassium (K_{ATP}) channels found in the outer membrane of pancreatic beta cells. Closure of these potassium channels causes opening of voltage-dependent calcium channels, followed by calcium influx which triggers cellular insulin release. These effects of the drug increase the sensitivity of islet beta cells to elevated levels of glucose, producing a greater insulin release at the same levels of plasma glucose.

Metformin HCl (Glucaphage) is an insulin sensitizer which improves both basal and postprandial plasma glucose in patients with type 2 diabetes. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Metformin is an oral anti-diabetic drugs; it has pharmacologic actions different from any other class of glucose lowering drugs. It's effective due to its actions of reducing insulin resistance, particularly in the liver and to a lesser extent in the peripheral tissues such as fat and adipose tissues. Metformin reduces hepatic gluconeogenesis and thereby lowers hepatic glucose output. Pharmacological actions of metformin have little or no effect upon insulin secretion but typically result in a reduction of both basal and postprandial blood glucose levels, reducing the physiological demands for insulin. This drug generally poses little risk of hypoglycemia since it does not elevate insulin levels. Its pharmacological actions are directed towards the liver than the adipose tissue.

Currently oral combination therapies that are used to lower blood glucose in type 2 patients employ insulin secretagogue + insulin sensitizer such as metformin or thiazolidinedione, or a combination of two insulin sensitizer with differing mechanisms (such as metformin + thiazolidinedione). In US, prandin (repaglinide) is indicated for combination therapy with metformin as separate formulations to lower blood glucose in patients whose hyperglycemia can not be controlled by diet and exercise plus monotherapy with any of the following agents such as metformin, sulfonylureas, or thiozolidinediones. The combination of these two drugs (repaglinide + metformin) has been studied under IND 70,959.

Repaglinide is administered just prior to major mealtime. Its elimination half life is brief (1 hour); its treatment strategy is different from sulphonylurea insulin secretagogues which have longer elimination half-life. In contrast, metformin has a plasma elimination half life of 6.2 hrs; its elimination half life in blood is longer (17.6 hours). Steady state plasma concentration of metformin is reached within 24-48 hrs. Both repaglinide and metformin are commonly administered at a meal time to prevent hypoglycemia (in the case of repaglinide) and minimize GI irritation (in the case of metformin). These two agents are metabolized/excreted differently, repaglinide mostly by hepatic metabolism and metformin primarily by renal excretion.

Thus, this combination provides increased insulin secretion and increased physiological response to insulin as well as the greater clinical glucose lowering effect than either agent alone. The recommended dose range for repaglinide is 0.5 to 4.0 mg. The recommended doses of metformin range from 500 to 2500 mg/day. The current application would combine the two agents (i.e. repaglinide/metformin) in a single tablet to be administered at two or more mealtimes per day as oral anti-diabetic agent.

This NDA 22-232 application is a 505(b)(2) application. The relevant information for repaglinide is available in NDA 20-741 and for metformin in DMF —— These two drugs are combined here in a fixed dose formulation. b(4)

Therefore, for the pre-clinical studies, sponsor states the following:

Module 4 – Non-clinical Study Reports and its related sections are not included in this submission as each of the active ingredients repaglinide and metformin HCl have been separately approved for over five years, thus affirming that these products are safe and effective. According to FDA guidance, "Because each of the products already is separately approved and there are studies by one or more of the innovator sponsors showing that the products can be safely and effectively used together, no new preclinical or safety and efficacy data would be needed for the application for the fixed dose combination" (Guidance for Industry – Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV).

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Currently the combination use of repaglinide + metformin is approved for type 2 diabetes in patients whose diabetes is not adequately controlled with either agent alone. The clinical glucose lowering action of repaglinide/metformin combination appears to be greater than those of either agent alone and safety of such a combination has been in general shown to be acceptable.

No pre-clinical toxicity studies are provided with these two drugs in combination. The doses of these two are going to be used at levels which are currently approved doses for repaglinide and metformin. The recommended dose range for repaglinide is 0.5 to 4.0 mg (NDA 20-741 for repaglinide); and for metformin is from 500 to 2500 mg/day (NDA 20-357 and NDA 21-202 for metformin). As indicated earlier there is extensive clinical experience with both repaglinide and metformin in humans. Sponsor has submitted this application as a 505b(2), which relies on the previous pharmacology/toxicology studies of repaglinide and metformin. Therefore, there appears to be no specific pharmacology/toxicity concern beyond those already outlined in the above NDAs. Therefore only label which is submitted in the PLR format is reviewed here.

Labeling Review: The pharmacology toxicology labeling in general is similar to the approved repaglinide and metformin labels. In the current application the submitted PLR label is reviewed and reviewer's recommended changes are stated below.

A. Following is sponsor's proposed label from 10/19/07 submission:

b(4)

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Pharm/Tox- 1

b(4)

External Recommendation: From the preclinical standpoint, approval of this application is recommended, pending labeling changes.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____
Concurrence Yes ___ No ___

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/misbin/marchic
Review code: AP
File name: nda22232 (PrandiMet combination of repaglinide +metformin)

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

/s/

Indra Antonipillai
5/20/2008 08:57:20 AM
PHARMACOLOGIST

From the pharm/tox point of view, this application is recommend for approval pending labeling changes.
This application is recommended for approval pending labeling changes

Karen Davis-Bruno
5/20/2008 08:59:19 AM
PHARMACOLOGIST

Signed off in DFS on 9/26/07

45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

NDA: 22-232: This NDA [redacted] application and submitted as an eCTD submission. b(4)
Submission date: 8/15/07
Sponsor: Novo Nordisk, Princeton, NJ.
Drug: PrandiMet tablets (code name NN 4440). It is a fixed dose combination product of two drugs repaglinide and metformin HCl at two strengths (1/500 and 2/500 mg/day repaglinide/metformin HCl respectively).

Introduction: Repaglinide is a short acting insulin seceretagogue indicated for the management of type 2 diabetes. It lowers the blood glucose by stimulating the release of insulin from pancreas. This effect is dependent on functioning beta cells in the pancreatic islets. Repaglinide is an inhibitor of potassium currents of ATP-sensitive potassium (K_{ATP}) channels found in the outer membrane of pancreatic beta cells. Closure of these potassium channels causes opening of voltage-dependent calcium channels, followed by calcium influx which triggers cellular insulin release.

Metformin HCl is an insulin sensitizer which improves both basal and postprandial plasma glucose in patients with type 2 diabetes. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin has little or no effect upon insulin secretion but because it reduces both basal and postprandial blood glucose levels, it reduces the physiological demand for insulin.

Both repaglinide (NDA 20-741) and metformin (DMF [redacted]) are approved drug products and commonly administered at a meal time to prevent hypoglycemia (in the case of repaglinide) and minimize GI irritation (in the case of metformin). These two agents are metabolized/excreted differently, repaglinide mostly by hepatic metabolism and metformin primarily by renal excretion. b(4)

The current application combines these two agents (i.e. repaglinide/metformin) in a single tablet to be administered at two or more mealtimes per day as oral anti-diabetic agent. The fixed dose combination (FDC) of these two drugs repaglinide/metformin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with either agent is not adequately controlled.

ITEM: NDA 22-232	**YES**	**NO**	**COMMENT**
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	Yes		

2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	Yes		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc)?	Yes		Sponsor refers to the previously marketed individual approved drug products, i.e. repaglinide (NDA 20-741) and metformin (DMF ——, approved) and has therefore not provided any pharmacology/toxicology data. However sponsor has conducted a pharmacokinetic interaction study of repaglinide and metformin in humans showing similar bioequivalence with the combination as for the individual drugs. b(4)
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)	Yes		Have electronic files of the carcinogenicity studies been submitted for statistical review? No carcinogenicity or other preclinical studies have been conducted with the current fixed dose combination drug, since the individual drugs repaglinide (NDA 20-741) and metformin (DMF ——are approved drug products. b(4)

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?			No non-clinical studies have been conducted under this NDA 22-232 as stated above.

6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	Yes		The excipients generally used in the formulation conform to a compandial standard. Repaglinide [redacted] contains [redacted] of meglumine [redacted], which has been used previously in FDA approved oral tablets at doses up to [redacted] Similarly, the current drug product contains [redacted] of polacrillin potassium ([redacted], which has also been used previously in other approved drug products at doses up to [redacted] (NDA 72-437 and NDA 73-449, from an FDA Inactive Ingredient Guide, January 1996).
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	Yes		The route of administration of the approved drug products and the current fixed dose combination product is oral .
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	Yes		Yes, the draft pharmacology/toxicity labeling submitted in general is in accordance with CFR and is similar to the approved repaglinide or metformin labels, and data express human dose multiples in mg/m^2 or AUC

b(4)

ITEM	YES	NO	COMMENT

9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	Yes		There are no CMC issues related to impurities/degradants or formulation changes. The sponsor in the current application (cover letter) states that no new pre-clinical or safety and efficacy data would be needed for the FDC application (guidance for Industry-Fixed dose combination and co-packaged drug products for treatment of HIV). In the submitted IND 70,959 on this FDC, similar formulation was proposed (see DFS review).
10) Reasons for refusal to file: Not applicable			

Reviewing Pharmacologist: Indra Antonipillai, DMEP
Supervisory Pharmacologist: Karen Davis-Bruno
File name: 22232-filing.

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

/s/

Indra Antonipillai
9/26/2007 12:04:10 PM
PHARMACOLOGIST
From the pharm/tox point of view this NDA application is filable
This application is filable

Karen Davis-Bruno
9/26/2007 12:05:40 PM
PHARMACOLOGIST