CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-386

SUMMARY REVIEW

Division Director's Memo

NDAs:	22-232 (original/ ——— b(4) 22-386 (resubmission) b(4)
Drug Product:	PrandiMet (fixed-dosed combination of repaglinide/metformin)
Applicant:	Novo Nordisk

Introduction

Novo Nordisk has submitted an NDA for the fixed-dosed combination (FDC) tablets containing repaglinide and metformin HCl. The proposed tradename is PrandiMet®. The formulation consists of the following dosage strengths, expressed as replaglinide/metformin HCl: 1-mg/500-mg and 2-mg/500-mg.

Prandin® (repaglinide) is available in 0.5-mg, 1-mg, and 2-mg dosage strengths with a recommendation to take with a meal. Patients not previously treated with an anti-diabetic agent or who have a HbA1c < 8% are advised to initiate therapy at the lowest dose of 0.5-mg whereas previously-treated patients or those who have HbA1c ≥ 8% can initiate therapy at the 1- or 2-mg dose. These recommendations were intended to minimize the risk of hypoglycemia in patients naïve to drug therapy or who had mild disease.

Metformin HCl was approved in 1995 and has had extensive clinical experience as monotherapy and in combination with multiple anti-diabetic agents. Several generic formulations are available with multiple dosage strengths including the 500-mg, 850-mg, and 1000-mg tablets. In the United States, the 500-mg dosage strength and its multiple are more commonly prescribed with the maximum recommended dose of 2.5g daily. Effective therapy is considered at doses ≥ 1 gram daily.

Prandin® was approved in 1997 as an adjunct to diet and exercise to lower blood glucose in patients with type 2 diabetes. In addition, Prandin® is indicated for combined use with metformin HCl to lower blood glucose in patients whose hyperglycemia is inadequately controlled by diet, exercise and either metformin HCl or repaglinide monotherapy. In other words, the combined use of repaglinide with metformin HCl is recommended only in patients who have failed monotherapy with either agent alone. The approval of a FDC tablet containing repaglinide and metformin HCl for this same indication would therefore only require a bioequivalence study showing relatively comparable pK between the FDC tablet and the two drugs co-administered to allow bridging to any clinical studies which used the repaglinide and metformin HCl as co-administered drug products. To this end, the applicant conducted a pivotal BE study and also submitted the clinical results of a study previously reviewed under the original NDA (Study AGEE-053).

b(4)

b(4)

The Division intends to take separate actions for [redacted] however, a single director's memo will be written to summarize the findings from the clinical studies and the different actions taken. b(4)

Clinical Studies Submitted in Support of Indication(s)
This memo will summarize the findings from three studies.

NN4440-1753 is the pivotal BE trial reviewed by Dr. Vaidyanathan from the Office of Clinical Pharmacology. This study established the bridge between the FDC drug product and the individual components, repaglinide and metformin HCl, coadministered. Please see the section below on *Clinical Pharmacology* for a discussion of this study and its results.

AGEE 053 is a 24-week efficacy and safety study that has been reviewed by the FDA under the original NDA (20-741) for Prandin® and was the basis for the current indication for use of Prandin in combination with metformin in patients who have no achieved adequate glycemic control with either repaglinide or metformin monotherapy.

This trial enrolled patients with type 2 diabetes who had HbA1c > 7% despite treatment with metformin for at least 6 months. Patients were randomized to received repaglinide added-on to metformin, repaglinide monotherapy (i.e., they were switched from metformin to repaglinide), or continue on metformin monotherapy. The mean dose of metformin at Baseline was approximately 1.8 g, hence it appears that the majority of patients were receiving an efficacious dose of metformin.

Page 11 of Dr. Misbin's medical officer review describes the titration scheme in this trial.

AGEE-3017 was a 16-week, open-label study in treatment-naïve patients with type 2 diabetes comparing repaglinide + metformin combination therapy to gliclazide (a sulfonylurea not approved in the U.S.) monotherapy and metformin monotherapy. The trial included a 4-week run-in period followed by a 4-week dose-titration period and a 12-week maintenance period.

Patients were eligible if they had a diagnosis of diabetes for at least 3 months and had not received any drug therapy for at least 3 months. HbA1c at randomization had to be between 7-12%. Initial doses of drug treatment were as follows.

- Repaglinide/metformin arm: 0.5-mg/500-mg (repaglinided was dosed tid with meals while the metformin once daily was administered with dinner)
- Gliclazide monotherapy: 80 mg daily
- Metformin monotherapy: 500 mg bid.

Page 5 of Dr. Misbin's medical officer review describes the dose titration scheme.

The primary efficacy endpoint measure was change in HbA1c from Baseline at Week 16. 322 patients were randomized in a 2:1:1 fashion to the combination therapy (n=163): gliclazide monotherapy (n=77): metformin monotherapy (n=81). Across all three treatment groups, approximately 20% discontinued/withdrew. The intent-to-treat (ITT) population was defined as all patients randomized who received at least one dose of medication and had at least one study

visit after study initiation. Primary efficacy analyses were performed on the ITT population. However, efficacy results were similar in both the ITT and per-protocol population.

The primary efficacy comparison was between the combination treatment group and the monotherapy groups; however, the study was not powered to show a difference between the combination treatment group and the individual monotherapy groups. Instead the gliclazide and metformin monotherapy groups were combined and efficacy was compared between these two pooled groups and the repaglinide/metformin combination group. This analysis is problematic as a FDC tablet considered for use over monotherapy should offer superiority in efficacy over the individual components. Furthermore, this trial did not include a repaglinide monotherapy arm. As a result, no conclusions can be made from this trial whether initiation of PrandiMet in drug-naïve patients would offer greater efficacy than initiation of repaglinide monotherapy.

Please see page 10 of Dr. Choudhury's review which summarizes the baseline demographics and patient characteristics in Studies 053 and 3017. The most notable differences between the two study populations were age and BMI with a lower mean age and BMI for patients in Study 3017, likely reflecting the treat-naïve population with a shorter duration of diabetes. Mean Baseline HbA1c in Study 053 was 8.5% compared to 9.0% in Study 3017.

Efficacy Findings (See Dr. Choudhury's statistical review dated 6/2/08 for details of efficacy findings)

AGEE 053

In patients with type 2 diabetes inadequately treated with metformin, the addition of repaglinide resulted in significantly greater reductions in HbA1c from Baseline than the continued use of metformin or repaglinide monotherapy.

The following table from Dr. Choudhury's table summarizes these efficacy findings.

Changes in HbA1c (%) from Baseline to End-of-Trial: Study AGEE/DCD/053/AUS

	Mean (SEM)	95% CI
ANOVA of HbA_{1c} changes, No Adjustment		
Repaglinide/Metformin	-1.41 (0.23)	[-1.87, -0.95] *
Repaglinide	-0.38 (0.23)	[-0.84, 0.08]
Metformin	-0.33 (0.24)	[-0.80, 0.15]
Repaglinide/Metformin – Repaglinide	-1.03 (0.32)	[-1.78, -0.29] *
Repaglinide/Metformin – Metformin	-1.08 (0.33)	[-1.84, -0.33] *
ANOVA of HbA_{1c} changes Adjusting for Centre		
Repaglinide/Metformin	-1.40 (0.23)	[-1.86, -0.94] *
Repaglinide	-0.34 (0.23)	[-0.80, 0.13]
Metformin	-0.32 (0.25)	[-0.81, 0.18]
Repaglinide/Metformin – Repaglinide	-1.06 (0.32)	[-1.81, -0.32] *
Repaglinide/Metformin – Metformin	-1.08 (0.33)	[-1.84, -0.33] *

* Statistically significant, $p < 0.05$

AGEE-3017

Repaglinide/metformin combination therapy resulted in a significant reduction in HbA1c from Baseline to Week 16 in patients who were naïve to drug therapy. The table below from Dr. Choudhury's review reveals superior efficacy of the combination arm to metformin monotherapy but the overlapping 95% CI around the LS Mean for the repaglinide/metformin and gliclazide arms would not support a conclusion of superior efficacy of the combination drug therapy over monotherapy with this sulfonylurea.

Table 1. Primary Efficacy Results as Summarized in Dr. Choudhury's FDA Statistical Review

Analysis of Changes in HbA1c (%) from Visit 2 to Visit 6, Study AGEE-3017

	N	LS Mean (SE)	95% CI
Analysis of HbA_{1c} changes, No Adjustment			
Repaglinide/Metformin	148	-2.134 (0.11)	[-2.342, -1.926]
Gliclazide	70	-1.920 (0.15)	[-2.223, -1.617]
Metformin	78	-1.387 (0.15)	[-1.674, -1.100]
Repaglinide/Metformin – Gliclazide		-0.214 (0.19)	[-0.581, 0.154]
Repaglinide/Metformin – Metformin		-0.747 (0.18)	[-1.101, -0.392] *
Analysis of HbA_{1c} changes, Adjusting for Centre			
Repaglinide/Metformin	148	-2.029 (0.12)	[-2.261, -1.796]
Gliclazide	70	-1.819 (0.16)	[-2.135, -1.502]
Metformin	78	-1.275 (0.15)	[-1.570, -0.980]
Repaglinide/Metformin – Gliclazide		-0.210 (0.18)	[-0.565, 0.145]
Repaglinide/Metformin – Metformin		-0.754 (0.17)	[-1.096, -0.412] *

*: Statistically significant, $p < 0.001$.

Safety Findings

Dr. Misbin's review of safety focused on the 2 clinical studies, 053 and 3017, and Study 1794 submitted at the 4-month safety update. Study 1794 compared PrandiMet to Avandamet.

Overall, the incidence of hypoglycemia is higher with PrandiMet compared to repaglinide or metformin monotherapy and Avandamet. In Study 053, 33.3% of the combination treatment group experienced a hypoglycemic episode – 3-fold higher than the repaglinide monotherapy group (10.7%). There were no reports of hypoglycemia in the metformin group in this study. Similarly, in Study 3017, symptomatic hypoglycemia was higher in the repaglinide/metformin group (24%) compared to metformin (5%) or gliclazide (9%). Hypoglycemia with confirmed BG measure of < 52 mg/dL was observed in 4% of the repaglinide/metformin group compared to none in the monotherapy groups and a major hypoglycemic episode was documented in the combination drug group.

Weight gain was also greater in the repaglinide/metformin group compared to metformin monotherapy.

These safety findings are not unexpected and is also an inherent risk of repaglinide. However, the more exaggerated risk of hypoglycemia with combination therapy should be noted in labeling. b(4)

Pharmacology/Toxicology
There were no new non-clinical studies submitted with this NDA. Since both components of this FDC tablet are approved drug products and toxicity studies have been conducted with these drugs under previous NDAs no additional preclinical studies were required.

Clinical Pharmacology (Please see Dr. Vaidyanathan's review dated 5/30/08)
NN4440-1753 was a single-blind, randomized, 3-period, crossover study with the primary objective of demonstrating bioequivalence between the FDC 2/500 mg tablet and coadministered 2-mg repaglinide with 500-mg metformin. The trial enrolled 55 healthy male and female volunteers who were randomized to two different treatment sequences of AAC or CBC wherein A represented the 2/500 FDC tablet, B represented the co-administered 2-mg repaglinide + 500-mg metformin, and C represented the 1/500 FDC tablet. Drug was administered immediately before a high-fat breakfast on Day 1, 7±3 and 14±3 of the study. PK sampling was performed pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 18, and 24 hrs after dosing.

The FDC tablet was found to be bioequivalent to the two drugs coadministered with respect to AUC_{inf}, AUC_{0-24}, AUC_{0-t}, and Cmax for both repaglinide drug levels and metformin drug levels. Dose proportionality was demonstrated between the 1/500 FDC tablet and 2/500 FDC tablet with respect to repaglinide drug levels and the metformin AUC and Cmax were bioequivalent between the two FDC tablets.

CMC
Please see Dr. Markofsky's CMC review dated 5/6/08 where he recommends approval of the FDC tablets. The FDC tablet will be approved with an 18-month expiry when the product is not stored above 25°C. Extension of the expiry date can be proposed in an Annual Report with supporting data.

Inspection of the testing and manufacturing facilities were found to be acceptable on June 18, 2008.

OSE Consults
DMETs has recommended against the proposed tradename, PrandiMet. Dr. Misbin's review has provided reasonable arguments for accepting PrandiMet and I concur with his recommendation to allow PrandiMet as the tradename. DMETs has also recommended against the italicizing of the metformin component in the tradename (Prandi*Met*). I concur with DMETs on this point as I believe there is sufficient emphasis through the uppercase "M" to relay that this is a combination drug product.

Other Regulatory/Administrative Issues
Administrative Filings
This application was originally submitted under NDA 22-232 for the fixed-dosed combination (FDC) tablets containing repaglinide and metformin on August 15, 2007, with a user-fee goal date of June 15, 2008. b(4)

Novo Nordisk resubmitted the identical supporting information

under a different NDA for the approval of the FDC tablets under NDA 22-386. The same user fee goal date was retained.

[redacted] b(4)

- NDA 22-386 is the application specific for the approval of the FDC tablets.
- [redacted] b(4)

Please note that discipline reviews for these data may have been electronically filed under these different NDA numbers [redacted] b(4)

Pediatrics

[redacted] because of concerns of weight gain, hypoglycemia, and a theoretical increased risk of cardiovascular adverse events. These safety concerns cannot be overlooked with any expectation of improved efficacy over other approved therapies in the pediatric population. PrandiMet was also discuss with the Pediatric Review Committee (PeRC) and the concerns raised for Prandin were carried over to PrandiMet. As such, pediatric study requirements have been waived for PrandiMet. b(4)

Financial Disclosure

See Section 4.4 of Dr. Misbin's review. No issues related to financial or equity interests on the part of investigators were identified which might invalidate the study results submitted to this NDA.

DSI

DSI inspection was requested for the pivotal BE study and were found to be acceptable.

Postmarketing Studies

No postmarketing studies are required nor are there any safety issues requiring consideration of a Risk Evaluation and Mitigation Strategy for the approval of this FDC tablet.

Labeling

Labeling for PrandiMet was restricted to an indication in patients with type 2 diabetes who failed to achieve adequate glycemic control with either agent alone. [redacted] b(4)

See final approved label under NDA 22-386.

Recommendations

Approval of fixed-dose combination product under NDA 22-386.

[redacted] b(4)

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

/s/

Mary Parks
6/23/2008 04:16:38 PM
MEDICAL OFFICER
This decisional memo discusses for b(4)
PrandiMet