Approval Package for:

APPLICATION NUMBER:
NDA 20-741/ S-030

Name: Prandin Tablets

Generic Name: Repaglinide

Sponsor: Novo Nordisk Pharmaceuticals, Inc

Approval Date: June 19, 2006
**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:**

NDA 20-741/S-030

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NDA 20-741/ S-030

APPROVAL LETTER
NDA 20-741/S-030

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your supplemental new drug application (sNDA) dated December 22, 2005, received December 23, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prandin (repaglinide) Tablets.

We acknowledge receipt of your submissions dated May 12 and June 14, 2006.

This supplement provides for changes to the package insert to include additional information in the CLINICAL PHARMACOLOGY Section, Pharmacokinetics and Drug-Drug Interactions subsections, and the PRECAUTIONS Section, Drug-Drug Interactions subsections based on data from two in vitro studies, one with trimethoprim and a second with rifampin. This application also includes additional adverse events in the ADVERSE REACTIONS section, in response to our letter issued March 15, 2006.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for package insert submitted on June 14, 2006).

Please submit an electronic version of the FPL according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved supplement NDA 20-741/S-030." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:
MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at (301) 796-1168.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Acting Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert
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
6/19/2006 09:12:26 PM
control in type 2 diabetes has not been definitively established to be effective in preventing the long-term complications of diabetes in patients with type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) has been conducted to indicate major glycemic control, as reflected by HbA1C, and fasting glucose levels, is associated with a reduction in complications requiring nephropathy, neuropathy, and retinopathy.

**CONTRADICTIONS**

Hypoglycemia may be severe in patients who are taking PRANDIN and gemfibrozil should not be taken in combination. See CLINICAL PHARMACOLOGY, Drug Interactions.

The hypoglycemic action of oral blood glucose-lowering agents may be potentiated by certain drugs including non-steroidal anti-inflammatory agents such as salicylates, aspirin, chlorpromazine, cimetidine, procainamide, pyrazinamide, quinidine, sulfonamides, and others. When such drugs are administered to a patient requiring PRANDIN and gemfibrozil, the response should be observed closely for hypoglycemia. When such drugs are administered to a patient receiving PRANDIN and gemfibrozil, the dosage of the hypoglycemic agents may need to be decreased.

Certain drugs tend to produce hypoglycemia and may need to be decreased in dosage in patients requiring PRANDIN and gemfibrozil. These drugs include the sulfonamides, the thiazides and other diuretics, corticosteroids, thyroid hormones, anticoagulants, phenytoin, niacinamide, niacin acid, and sympathomimetics. In some patients treated with the sulfonylurea drugs and glucocorticoids, the patient should be observed closely for signs of hypoglycemia. When drugs are administered to a patient receiving PRANDIN and gemfibrozil, the response should be observed closely for signs of hypoglycemia.

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APPLICATION NUMBER:
NDA 20-741/S-030

Clinical Pharmacology/Biopharmaceutics
Review(s)
OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 20-741 (SLR-030) Submission Date(s): 12/22/05
Brand Name Prandin®
Generic Name Repaglinide
Reviewers Jaya bharathi Vaidyanathan, Ph.D.
Team Leader Hae-Young Ahn, Ph.D.
OCP Division DCP-2
ORM division Division of Metabolic and Endocrine Products
Sponsor Novo Nordisk
Submission Type; Code Prior Approval Labeling supplement
Formulation; Strength(s) 0.5, 1 and 2 mg tablets
Indication To treat type 2 diabetes

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I. Executive Summary

Novo Nordisk has submitted a prior-approval labeling supplement to the NDA 20-741 for Prandin (repaglinide). Repaglinide is approved for the treatment of type 2 diabetes. The changes in the label are based on the sponsor’s two in vitro studies in human hepatocytes as well as recent publications of studies conducted in healthy volunteers by independent
investigators. The changes in the label are to address the influence of rifampin and trimethoprim on repaglinide's pharmacokinetic profile when concomitantly administered. Additionally, sponsor has included information on the involvement of CYP2C8 in the metabolism of repaglinide.

A  Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DCPB-2) has reviewed NDA 20-741 SLR-030 submitted on 22 December 2005 and finds it acceptable. Recommendations about labeling comments on page 8 should be sent to sponsor as appropriate.

B  Phase IV Commitments

Not applicable.

C  Summary of CPB Findings

The proposed biotransformation pathway for repaglinide is depicted in Figure 1.

Figure 1: Chemical structure of repaglinide and its proposed metabolic pathway in humans.
The two in vitro studies reviewed here were performed by the sponsor in order to characterize the metabolism of repaglinide.

In vitro metabolism of repaglinide in human liver microsomes:
The metabolites formed in human liver microsomes did not correlate to that observed in vivo. The principal CYP450 enzyme involved in the metabolism of repaglinide was identified as CYP3A4. This was based on correlation with CYP3A4 activity in the liver microsomes as well as inhibition by ketoconazole (23-89% inhibition). CYP2C9 was also shown to contribute to the metabolism of repaglinide to some extent.

Effect of clarithromycin, troleandomycin and ketoconazole on the in vitro metabolism of repaglinide:
The metabolites formed in human hepatocytes correlated to that observed in vivo. Therefore human hepatocytes were found to be a better predictive tool for repaglinide metabolism as compared to human liver microsomes. The effect of the different inhibitors of CYP3A4 including clarithromycin (100 μM), troleandomycin (100 μM) and ketoconazole (1 μM) on the total metabolism of repaglinide was limited. The effect was mainly on one of the metabolite M2. Incubations with ketoconazole (100 μM) almost totally inhibited the metabolism of repaglinide, indicating that CYP2C8 is the most important CYP isoform for the metabolism of repaglinide.

II QBR

A General Attributes

Not applicable.

B General Clinical Pharmacology

Not applicable.

C Intrinsic Factors

Not applicable.
D Extrinsic Factors

Drug-drug interactions:

Which CYP450 enzymes are involved in the metabolism of repaglinide in humans?

The metabolism of repaglinide was determined in the following two studies.

**Study 960144:** *In vitro* studies using human liver microsomes were conducted to identify the principal CYP450 enzyme isoforms involved in the metabolism of repaglinide. Repaglinide was metabolized into a number of metabolites *in vitro* of which the four major ones were termed HLM-1, HLM-2, HLM-3 and HLM-4. None of these metabolites corresponded to the previously reported *in vivo* metabolites of repaglinide (the retention times were different than that of the repaglinide metabolites M1, M2, M5, M6 or M12 which have been isolated from a previous human study). Therefore it is likely that the *in vitro* formed metabolites could not be isolated from *in vivo* since they may be too unstable and possibly undergo further biotransformation to M2 and M1. Also literature report indicates that these in vitro metabolites cannot be transformed into *in vivo* human metabolites M5, M6 and M12.

The formation of all the metabolites was linear up to substrate concentration of 22 µM, and therefore it was not possible to define enzyme kinetic parameters such as K_m and V_{max} since this did not exhibit Michaelis-Menten kinetics in this concentration range.

**Figure 2:** Formation of microsomal metabolites as a function of repaglinide concentration (mean ± SD)

![Graph showing formation of microsomal metabolites](attachment:graph.png)

The correlation coefficient rates were highest when comparing the metabolite formation rates with total CYP450 enzyme activity as well as with CYP2A6, CYP2C9 and CYP3A4 activities.
Inhibitors were also tested for interaction with the formation of HLM metabolites in human liver microsomes. Ketoconazole (CYP3A4 inhibitor) exhibited significant inhibition at the concentration tested when used with low repaglinide concentration. There was no inhibition in liver microsomes with low CYP3A activity. HLM-4 formation was most markedly inhibited. At high repaglinide concentration, ketoconazole inhibited significantly the formation of HLM-4 (> 89% inhibition). There was limited inhibition of metabolite formation by sulfaphenazole (CYP2C9 inhibitor), inhibiting only against HLM-4 formation at high repaglinide concentration while there was no inhibition by quinidine (CYP2D6 inhibitor).

Metabolism was also conducted using single CYP450 enzymes expressed in human lymphoblastoid cell line. Only HLM-1 and HLM-2 were formed in CYP1A2 expressing membranes. Two alleles of CYP2C9 were tested and both alleles metabolized repaglinide, with CYP2C9Val forming only HLM-1 and CYP2C9Arg formed both HLM-1 and HLM-2. CYP3A4 formed all metabolites except HLM-1. Formation rates were much higher for this isofom than the others with HLM-2 formation being about 7 fold higher than that observed with CYP2C9Arg.

Comments:

- Metabolites formed in this study did not correlate to repaglinide metabolites formed in vivo.
- Two concentrations of repaglinide were used in this study: 0.55 μM, a concentration close to plasma concentration in humans following a dose of 4 mg t.i.d. and a higher concentration 22 μM, a concentration supposedly to represent the maximal in vivo concentration in the liver assuming high plasma to liver partition in humans.
- Inhibitors used in the study included; furaflaxine (CYP1A2), diethyldithiocarbamate (CYP2A6 and CYP2E1), sulfaphenazole (CYP2C9), S-mephenytoin (CYP2C19), quinidine (CYP2D6) and ketoconazole (CYP3A4).
- Repaglinide standard curve was calculated using the concentration range of 0.11-22 μM.
- Repaglinide and associated metabolites were identified using a reversed phase HPLC and on line radiochemical detection.
- Based on this study mainly CYP3A4 and possibly CYP2C9 (to a very small extent) are involved in the metabolism of repaglinide.

**Study 202275:** This study was conducted in order to determine the mechanism behind the increases in plasma concentration of repaglinide when dosed concomitantly with clarithromycin (CYP3A4 inhibitor). Previous in vitro study had suggested the involvement of CYP3A4 in the metabolism of repaglinide, however ketoconazole had limited effect on the metabolism in vivo (Hartorp V et al, Br J Clin Pharmacol, 2003). Human hepatocytes from 3 donors were chosen as the in vitro system to investigate the metabolism of repaglinide (5 μM). In addition to clarithromycin, two other CYP3A4 inhibitors were used: ketoconazole and troleandomycin.
Repaglinide was extensively metabolized to several metabolites with 4 major metabolites in hepatocytes from 3 different donors representing high, medium and low CYP3A4 activity. Unlike the previous study, the observed metabolites were similar to that seen in vivo. Following 1 h incubation of repaglinide (without inhibitor), 81%, 68% and 78% of repaglinide was metabolized to 8-10 metabolites in the three donors respectively. Troleandomycin and ketoconazole (low concentration) were only able to inhibit the formation of 1-2 metabolites. With clarithromycin, there was about 2-10 % decrease in repaglinide metabolism in the 3 hepatocyte preparations. High ketoconazole concentrations almost blocked the metabolism of repaglinide indicating involvement of CYP2C8 (Figure 3).

**Figure 3: Inhibition of repaglinide metabolism in the hepatocytes from 3 donors using different inhibitors:**

TAO = troleandomycin  
CLARI = clarithromycin  
KETO = ketoconazole
Comments:

- Clarithromycin and troleandomycin were pre-incubated for 30 min at 100 μM to allow for CYP3A4-complex formation before addition of C\(^{14}\)-repaglinide and incubation for 1 h. The inhibition of CYP3A4 activity was documented by separate incubations with testosterone as substrate. Ketoconazole was tested at 1, 10 and 100 μM, with the lowest concentration corresponding to CYP3A4 inhibition and higher concentrations corresponding to CYP2C8 inhibition.

- Overall, relatively small inhibitory effect of clarithromycin and other CYP3A4 inhibitors on repaglinide metabolism was observed in human hepatocytes. In contrast, Niemi M et al (Clin. Pharmacol. Ther., 2001) observed a 167% increase in C\(\text{max}\) and 140% increase in AUC of repaglinide (0.25 mg) following co-administration with clarithromycin in healthy volunteers. Also in other study in human volunteers, ketoconazole increased repaglinide (2 mg) C\(\text{max}\) and AUC by 105% and 115% respectively. The 0.25 mg used in one of the studies is sub-therapeutic dose, while the ketoconazole study used dose in the therapeutic range.

- Inhibition of metabolism at higher concentration of ketoconazole indicates that CYP2C8 is also an important CYP isoform in the metabolism of repaglinide.

E General Biopharmaceutics

Not applicable.

F Analytical

\(^{14}\)C-Repaglinide and its metabolite formed in incubations with human liver microsomes were analyzed by reversed-phase HPLC and detected using on-line radiochemical detector. Ionspray liquid chromatography mass spectrometry (LC-MS/MS) was performed to confirm the chemical structures of metabolites formed in human liver microsomes.
The repaglinide and its metabolites formed in human hepatocytes were analyzed by HPLC and detected using both UV detection at \( \lambda = 220 \) nm and online radiochemical detection. Major metabolites were identified by LC/MS/MS and MS/MS analysis on a ion-trap mass spectrometer equipped with an electrospray interface.

III Labeling Comments

The proposed changes to the Clinical Pharmacology section as well as precaution sections and the recommendations are as follows:

(Strikeout text is recommended to be deleted and underline text is recommended to be added.)

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<th>SECTIONS-subsections</th>
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<th>Recommended</th>
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<tr>
<td>CLINICAL PHARMACOLOGY – Pharmacokinetics, Metabolism</td>
<td>Repaglinide is completely metabolized by oxidative biotransformation and direct conjugation with glucuronic acid after either an IV or oral dose. The major metabolites are an oxidized dicarboxylic acid (M2), the aromatic amine (M1), and the acyl glucuronide (M7). The cytochrome P-450 enzyme system, specifically 2C8 and 3A4, have been shown to be involved in the N-dealkylation of repaglinide to M2 and the further oxidation to M1. Metabolites do not contribute to the glucose-lowering effect of repaglinide.</td>
<td>Proposed change is acceptable.</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Rifampin: Co-administration of 600 mg rifampin and a single dose of 4 mg PRANDIN (after 6 days of once daily rifampin 600 mg) resulted in a 32% and 26% decrease in repaglinide AUC and C&lt;sub&gt;max&lt;/sub&gt;, respectively. The decreases were from 40.4 ng/mL to 29.7 ng/mL for C&lt;sub&gt;max&lt;/sub&gt; and from 56.8 ng/mL<em>hr to 38.7 ng/mL</em>hr for AUC.</td>
<td>Rifampin: Co-administration of 600 mg rifampin and a single dose of 4 mg PRANDIN (after 6 days of once daily rifampin 600 mg) resulted in a 32% and 26% decrease in repaglinide AUC and C&lt;sub&gt;max&lt;/sub&gt;, respectively. The decreases were from 40.4 ng/mL to 29.7 ng/mL for C&lt;sub&gt;max&lt;/sub&gt; and from 56.8 ng/mL<em>hr to 38.7 ng/mL</em>hr for AUC. In another study, co-administration of 600 mg rifampin and a single dose of 4 mg PRANDIN (after 6 days of once daily rifampin 600 mg) resulted in a 48% and 17% decrease in repaglinide median AUC and median C&lt;sub&gt;max&lt;/sub&gt;, respectively. The median decreases were from 54 ng/mL<em>hr to 28 ng/mL</em>hr for AUC and from 35 ng/mL to 29 ng/mL for C&lt;sub&gt;max&lt;/sub&gt;. PRANDIN administered by itself (after 7 days of once daily rifampin 600 mg) resulted in an 80% and 79% decrease in repaglinide median AUC and C&lt;sub&gt;max&lt;/sub&gt; respectively. The decreases were from 54 ng/mL<em>hr to 11 ng/mL</em>hr for AUC and from 35 ng/mL to 7.5 ng/mL for C&lt;sub&gt;max&lt;/sub&gt;.</td>
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<tr>
<td>CLINICAL PHARMACOLOGY – Drug-Drug Interactions, Rifampin</td>
<td>Trimethoprim: Co-administration of 160 mg trimethoprim and a single dose of 0.25 mg PRANDIN (after 2 days of twice daily and one dose on the third day of trimethoprim 160 mg) resulted in a 61% and 41% increase in repaglinide AUC and C&lt;sub&gt;max&lt;/sub&gt; respectively. The increase in AUC was from 5.9 ng/mL<em>hr to 9.6 ng/mL</em>hr and the increase in C&lt;sub&gt;max&lt;/sub&gt; was from 4.7 ng/mL to 6.6 ng/mL.</td>
<td>Proposed change is acceptable.</td>
</tr>
<tr>
<td>PRECAUTIONS – Drug-Drug Interactions</td>
<td><em>In vitro</em> data indicate that PRANDIN is metabolized by cytochrome P450 enzymes 2C8 and 3A4. Consequently, repaglinide metabolism may be altered by drugs which influence these cytochrome P450 enzyme systems via induction and inhibition. Caution should therefore be used in patients who are on PRANDIN and taking inhibitors and/or inducers of CYP2C8 and CYP3A4. The effect may be very significant if both enzymes are inhibited at the same time resulting in a substantial increase in repaglinide plasma concentrations. Drugs that are known to inhibit CYP3A4 include antifungal agents like ketoconazole, itraconazole, and antibacterial agents like erythromycin. Drugs that are known to inhibit CYP2C8 include agents like trimethoprim, gemfibrozil and montelukast. Drugs that induce the CYP3A4 and/or 2C8 enzyme systems include rifampin, barbiturates, and carbamezepine. See CLINICAL PHARMACOLOGY section, Drug-Drug Interactions.</td>
<td>Proposed change is acceptable.</td>
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**IV Proposed Label**

**PRANDIN**
(repaglinide) Tablets (0.5, 1, and 2 mg)
Rx only

**DESCRIPTION**

PRANDIN (repaglinide) is an oral blood glucose-lowering drug of the meglitinide class used in the management of type 2 diabetes mellitus (also known as non-insulin dependent diabetes mellitus or NIDDM). Repaglinide, S(+)-2-ethoxy-4-(2((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid, is chemically unrelated to the oral sulfonylurea insulin secretagogues.

The structural formula is as shown below:
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-741/s-030

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
Division of Metabolism and Endocrinology Products (DMEP)

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-741/S-030

Name of Drug: Prandin (repaglinide) Tablets

Applicant: Novo Nordisk, Inc.

Material Reviewed:

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<td>June 15, 2006</td>
<td>Revised Proposed Package Insert (PI)</td>
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<td>May 12, 2006</td>
<td>May 15, 2006</td>
<td>Revised Proposed PI</td>
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<tr>
<td>December 22, 2005</td>
<td>December 23, 2005</td>
<td>Proposed PI</td>
</tr>
</tbody>
</table>

Referenced Material:

Clinical pharmacology review by Jaya Vaidyanathan, Ph.D., dated May 9, 2006 (OCPB)

Office of Drug Safety (ODS) Postmarketing Safety Review by Joslyn Swann, R.Ph., dated October 25, 2005

Background and Summary

Prandin (repaglinide) Tablet is currently approved as adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus whose hyperglycemia cannot be controlled by diet and exercise alone. Prandin is also indicated for combination therapy in patients whose hyperglycemia cannot be controlled by diet and exercise plus monotherapy with any following agents: metformin, sulfonylureas, or thiazolidinediones. Prandin is NOT indicated for use with insulin (please refer to the reviews for S-022).

On December 22, 2005, Novo Nordisk submitted a “Prior Approval” supplement to revise the package insert. Proposed additions include additional information in the CLINICAL PHARMACOLOGY Section, Pharmacokinetics and Drug-Drug Interactions subsections, and the PRECAUTIONS Section, Drug-Drug Interactions subsections based on data from two in vitro studies, one with trimethoprim and a second with rifampin.
1. NN Study # 960144: In vitro metabolism of repaglinide (τ → ζ) and
2. NN Study #202275: In vitro investigations of the effect of clarithromycin,
troleandomycin and ketoconazole on the metabolism of repaglinide.

On March 15, 2006, DMEP issued a supplement request letter for the addition of the following postmarketing adverse events to be included in the ADVERSE REACTIONS section in the labeling: jaundice and ζ → θ hepatitis. This request was based on a recommendation from the Office of Drug Safety following their review, dated October 25, 2005, of postmarketing adverse events. Novo Nordisk agreed to this request and decided to submit a revised proposed package insert to S-030 instead of a new labeling supplement.

Upon further discussion, additional revisions were made to the label. The final agreed upon package insert was submitted on June 14, 2006.

Review

The revised proposed PI, submitted on June 14, 2006, was compared to the currently approved PI, approved with S-022 on February 10, 2005. The following revisions have been made, additions underlined and deletions noted by strikethrough:

CLINICAL PHARMACOLOGY
Pharmacokinetics
Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process
Conclusions

An approval letter should be drafted for this supplement. Since labeling will be approved on draft, sponsor will also be asked to submit FPL in the approval letter.
CSO LABELING REVIEW
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lina Aljuburi
6/19/2006 12:31:48 PM
CSO
NDA 20-741/S-030

PRIOR APPROVAL SUPPLEMENT

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Prandin (repaglinide) Tablets

NDA Number: 20-741

Supplement number: 030

Date of supplement: December 22, 2005

Date of receipt: December 23, 2005

This supplemental application proposes changes to the Prandin Package Insert in the CLINICAL PHARMACOLOGY Section, Pharmacokinetics and Drug-Drug Interactions subsections, and the PRECAUTIONS Section, Drug-Drug Interactions subsections.

We have filed this application on February 21, 2006, in accordance with 21 CFR 314.101(a). The user fee goal date is June 23, 2006.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltville, MD 20705-1266
If you have any question, please call me at (301) 796-1168.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Lina Aljuburi
3/13/2006 06:27:15 PM