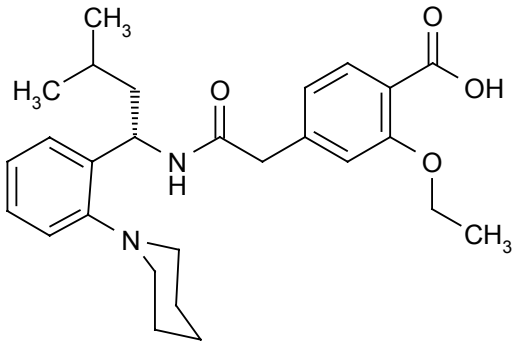
(repaglinide) Tablets (0.5, 1, and 2 mg)

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:



Repaglinide is a white to off-white powder with molecular formula C_{27} H_{36} N_2 O_4 and a molecular weight of 452.6. PRANDIN® tablets contain 0.5 mg, 1 mg, or 2 mg of repaglinide. In addition each tablet contains the following inactive ingredients: calcium hydrogen phosphate (anhydrous), microcrystalline cellulose, maize starch, polacrilin potassium, povidone, glycerol (85%), magnesium stearate, meglumine, and poloxamer. The 1 mg and 2 mg tablets contain iron oxides (yellow and red, respectively) as coloring agents.

CLINICAL PHARMACOLOGY

Mechanism of Action

Repaglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta (ß) cells in the pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations.

Repaglinide closes ATP-dependent potassium channels in the ß-cell membrane by binding at characterizable sites. This potassium channel blockade depolarizes the ß-cell, which leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion. The ion channel mechanism is highly tissue selective with low affinity for heart and skeletal muscle.

Pharmacokinetics

Absorption: After oral administration, repaglinide is rapidly and completely absorbed from the gastrointestinal tract. After single and multiple oral doses in healthy subjects or in patients, peak plasma drug levels (C_{max}) occur within 1 hour (T_{max}). Repaglinide is rapidly eliminated from the blood stream with a half-life of approximately 1 hour. The mean absolute bioavailability is 56%. When repaglinide was given with food, the mean T_{max} was not changed, but the mean C_{max} and AUC (area under the time/plasma concentration curve) were decreased 20% and 12.4%, respectively.

Distribution: After intravenous (IV) dosing in healthy subjects, the volume of distribution at steady state (V_{ss}) was 31 L, and the total body clearance (CL) was 38 L/h. Protein binding and binding to human serum albumin was greater than 98%.

Metabolism: 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 3A4, has 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.

Excretion: Within 96 hours after dosing with ^{14}C-repaglinide as a single, oral dose, approximately 90% of the radiolabel was recovered in the feces and approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound. The major metabolite (M2) accounted for 60% of the administered dose. Less than 2% of parent drug was recovered in feces.

Pharmacokinetic parameters: The pharmacokinetic parameters of repaglinide obtained from a single-dose, crossover study in healthy subjects and from a multiple-dose, parallel, dose-proportionality (0.5, 1, 2 and 4 mg) study in patients with type 2 diabetes are summarized in the following table:

Parameter	Patients with type 2 diabetes[a]
Dose 0.5 mg 1 mg 2 mg 4 mg	$AUC_{0\text{-}24\ hr}$ Mean ±SD (ng/mL*hr): 68.9 ±154.4 125.8 ±129.8 152.4 ±89.6 447.4 ±211.3
Dose 0.5 mg 1 mg 2 mg 4 mg	$C_{max0\text{-}5\ hr}$ Mean ±SD (ng/mL): 9.8 ±10.2 18.3 ±9.1 26.0 ±13.0 65.8 ±30.1
Dose 0.5 - 4 mg	$T_{max0\text{-}5\ hr}$ Means (SD) 1.0 - 1.4 (0.3 - 0.5) hr
Dose 0.5 - 4 mg	$T_{½}$ Mean (Ind Range) 1.0 - 1.4 (0.4 - 8.0) hr
Parameter	Healthy Subjects
CL based on i.v.	38± 16 L/hr
V_{ss} based on i.v.	31± 12 L
AbsBio	56± 9 %

a: dosed preprandially with three meals

CL = total body clearance
V_{ss} = volume of distribution at steady state
AbsBio = absolute bioavailability

These data indicate that repaglinide did not accumulate in serum. Clearance of oral repaglinide did not change over the 0.5 - 4 mg dose range, indicating a linear relationship between dose and plasma drug levels.

Variability of exposure: Repaglinide AUC after multiple doses of 0.25 to 4 mg with each meal varies over a wide range. The intra-individual and inter-individual coefficients of variation were 36% and 69%, respectively. AUC over the therapeutic dose range included 69 to 1005 ng/mL*hr, but AUC exposure up to 5417 ng/mL*hr was reached in dose escalation studies without apparent adverse consequences.

Special populations:
Geriatric. Healthy volunteers were treated with a regimen of 2 mg taken before each of 3 meals. There were no significant differences in repaglinide pharmacokinetics between the group of patients <65 years of age and a comparably sized group of patients ≥65 years of age. (See **PRECAUTIONS, Geriatric Use**)

Pediatric. No studies have been performed in pediatric patients.

Gender. A comparison of pharmacokinetics in males and females showed the AUC over the 0.5 mg to 4 mg dose range to be 15% to 70% higher in females with type 2 diabetes. This difference was not reflected in the frequency of hypoglycemic episodes (male: 16%; female: 17%) or other adverse events. With respect to gender, no change in general dosage recommendation is indicated since dosage for each patient should be individualized to achieve optimal clinical response.

Race. No pharmacokinetic studies to assess the effects of race have been performed, but in a U.S. 1-year study in patients with type 2 diabetes, the blood glucose-lowering effect was comparable between Caucasians (n=297) and African-Americans (n=33). In a U.S. dose-response study, there was no apparent difference in exposure (AUC) between Caucasians (n=74) and Hispanics (n=33).

Drug-Drug Interactions:
Drug interaction studies performed in healthy volunteers show that PRANDIN® had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline, or warfarin. Co-administration of cimetidine with PRANDIN® did not significantly alter the absorption and disposition of repaglinide.

Additionally, the following drugs were studied in healthy volunteers with co-administration of PRANDIN®. Listed below are the results:

Ketoconazole: Co-administration of 200 mg ketoconazole and a single dose of 2 mg PRANDIN® (after 4 days of once daily ketoconazole 200 mg) resulted in a 15% and 16% increase in repaglinide AUC and Cmax, respectively. The increases were from 20.2 ng/ml to 23.5 ng/ml for Cmax and from 38.9 ng/mL *hr to 44.9 ng/mL *hr for AUC.

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 Cmax, respectively. The decreases were from 40.4 ng/ml to 29.7 ng/ml for Cmax and from 56.8 ng/mL *hr to 38.7 ng/mL *hr for AUC.

Levonorgestrel & Ethinyl Estradiol: Co-administration of a combination tablet of 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol administered once daily for 21 days with 2 mg PRANDIN® administered three times daily (days 1-4) and a single dose on Day 5 resulted in 20% increases in repaglinide, levonorgestrel, and ethinyl estradiol $C_{max.}$ The increase in repaglinide Cmax was from 40.5 ng/ml to 47.4 ng/ml. Ethinyl estradiol AUC parameters were increased by 20%, while repaglinide and levonorgestrel AUC values remained unchanged.

Simvastatin: Co-administration of 20 mg simvastatin and a single dose of 2 mg PRANDIN® (after 4 days of once daily simvastatin 20 mg and three times daily Prandin 2 mg) resulted in a 26% increase in repaglinide Cmax from 23.6 ng/ml to 29.7 ng/ml. AUC was unchanged.

Nifedipine: Co-administration of 10 mg nifedipine with a single dose of 2 mg PRANDIN®

(after 4 days of three times daily nifedipine 10 mg and three times daily PRANDIN® 2 mg) resulted in unchanged AUC and Cmax values for both drugs.

Renal insufficiency. Single-dose and steady-state pharmacokinetics of repaglinide were compared between patients with type 2 diabetes and normal renal function (CrCl > 80 mg/dL), mild to moderate renal function impairment (CrCl = 40 – 80 mg/dL), and severe renal function impairment (CrCl = 20 – 40 mg/dL). Both AUC and C_{max} of repaglinide were similar in patients with normal and mild to moderately impaired renal function (mean values 56.7 ng/mL *hr vs 57.2 ng/mL *hr and 37.5 ng/mL vs 37.7 ng/mL, respectively.) Patients with severely reduced renal function had elevated mean AUC and C_{max} values (98.0 ng/mL *hr and 50.7 ng/mL, respectively), but this study showed only a weak correlation between repaglinide levels and creatinine clearance. Initial dose adjustment does not appear to be necessary for patients with mild to moderate renal dysfunction. **However, patients with type 2 diabetes who have severe renal function impairment should initiate PRANDIN® therapy with the 0.5 mg dose – subsequently, patients should be carefully titrated. Studies were not conducted in patients with creatinine clearances below 20 mg/mL or patients with renal failure requiring hemodialysis.**

Hepatic insufficiency. A single-dose, open-label study was conducted in 12 healthy subjects and 12 patients with chronic liver disease (CLD) classified by Child-Pugh scale and caffeine clearance. Patients with moderate to severe impairment of liver function had higher and more prolonged serum concentrations of both total and unbound repaglinide than healthy subjects ($AUC_{healthy}$: 91.6 ng/mL*hr; $AUC_{CLD\ patients}$: 368.9 ng/mL*hr; $C_{max,\ healthy}$: 46.7 ng/mL: $C_{max,\ CLD\ patients}$: 105.4 ng/mL). AUC was statistically correlated with caffeine clearance. No difference in glucose profiles was observed across patient groups. Patients with impaired liver function may be exposed to higher concentrations of repaglinide and its associated metabolites than would patients with normal liver function receiving usual doses. Therefore, **PRANDIN® should be used cautiously in patients with impaired liver function. Longer intervals between dose adjustments should be utilized to allow full assessment of response.**

Clinical Trials
A four-week, double-blind, placebo-controlled dose-response trial was conducted in 138 patients with type 2 diabetes using doses ranging from 0.25 to 4 mg taken with each of three meals. PRANDIN® therapy resulted in dose-proportional glucose lowering over the full dose range. Plasma insulin levels increased after meals and reverted toward baseline before the next meal. Most of the fasting blood glucose-lowering effect was demonstrated within 1-2 weeks.

In a double-blind, placebo-controlled, 3-month dose titration study, PRANDIN® or placebo doses for each patient were increased weekly from 0.25 mg through 0.5, 1, and 2 mg, to a maximum of 4 mg, until a fasting plasma glucose (FPG) level <160 mg/dL was achieved or the maximum dose reached. The dose that achieved the targeted control or the maximum dose was continued to end of study. FPG and 2-hour post-prandial glucose (PPG) increased in patients receiving placebo and decreased in patients treated with repaglinide. Differences between the repaglinide- and placebo-treated groups were -61 mg/dL (FPG) and -104 mg/dL (PPG). The between-group change in $HbA1_c$, which reflects long-term glycemic control, was

1.7% units.

PRANDIN® vs. Placebo Treatment: Mean FPG, PPG, and $HbA1_c$ Changes from baseline after 3 months of treatment:

	FPG (mg/dL)		PPG (mg/dL)		$HbA1_c$ (%)	
	PL	R	PL	R	PL	R
Baseline	215.3	220.2	245.2	261.7	8.1	8.5
Change from Baseline (at last visit)	30.3	-31.0*	56.5	-47.6*	1.1	-0.6*

FPG = fasting plasma glucose PPG = post-prandial glucose
PL = placebo (N=33) R = repaglinide (N=66)
* $p < 0.05$ for between group difference

Another double-blind, placebo-controlled trial was carried out in 362 patients treated for 24 weeks. The efficacy of 1 and 4 mg preprandial doses was demonstrated by lowering of fasting blood glucose and by HbA1c at the end of the study. $HbA1_C$ for the PRANDIN®-treated groups (1 and 4 mg groups combined) at the end of the study was decreased compared to the placebo-treated group in previously naïve patients and in patients previously treated with oral hypoglycemic agents by 2.1% units and 1.7% units, respectively. In this fixed-dose trial, patients who were naïve to oral hypoglycemic agent therapy and patients in relatively good glycemic control at baseline (HbA1c below 8%) showed greater blood glucose-lowering including a higher frequency of hypoglycemia. Patients who were previously treated and who had baseline HbA1c $\geq$ 8% reported hypoglycemia at the same rate as patients randomized to placebo. There was no average gain in body weight when patients previously treated with oral hypoglycemic agents were switched to PRANDIN®. The average weight gain in patients treated with PRANDIN® and not previously treated with sulfonylurea drugs was 3.3%.

The dosing of PRANDIN® relative to meal-related insulin release was studied in three trials including 58 patients. Glycemic control was maintained during a period in which the meal and dosing pattern was varied (2, 3 or 4 meals per day; before meals x 2, 3, or 4) compared with a period of 3 regular meals and 3 doses per day (before meals x 3). It was also shown that PRANDIN® can be administered at the start of a meal, 15 minutes before, or 30 minutes before the meal with the same blood glucose lowering effect.

PRANDIN® was compared to other insulin secretagogues in 1-year controlled trials to demonstrate comparability of efficacy and safety. Hypoglycemia was reported in16% of 1228 PRANDIN® patients, 20% of 417 glyburide patients, and 19% of 81 glipizide patients. Of PRANDIN® treated patients with symptomatic hypoglycemia, none developed coma or required hospitalization.

PRANDIN® was studied in combination with metformin in 83 patients not satisfactorily controlled on exercise, diet, and metformin alone. Combination therapy with PRANDIN® and

metformin resulted in synergistic improvement in glycemic control compared to repaglinide or metformin monotherapy. $HbA1_c$ was improved by 1% unit and FPG decreased by an additional 35 mg/dL.

PRANDIN® and Metformin Therapy: Mean $HbA1_C$ and FPG Changes from Baseline after 3 Months Treatment

	PRANDIN®	Combination	Metformin
N	28	27	27
$HbA1_c$ (% units)	-0.38	-1.41*	-0.33
FPG (mg/dL)	8.8	-39.2*	-4.5

* p<.05, for pairwise comparisons with Prandin® and metformin.

INDICATIONS AND USAGE

PRANDIN® is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone.

PRANDIN® is also indicated for use in combination with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by exercise, diet, and either repaglinide or metformin alone. If glucose control has not been achieved after a suitable trial of combination therapy, consideration should be given to discontinuing these drugs and using insulin. Judgments should be based on regular clinical and laboratory evaluations.

In initiating treatment for patients with type 2 diabetes, diet and exercise should be emphasized as the primary form of treatment. Caloric restriction, weight loss, and exercise are essential in the obese diabetic patient. Proper dietary management and exercise alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. In addition to regular physical activity, cardiovascular risk factors should be identified and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral blood glucose-lowering agent or insulin should be considered. Use of PRANDIN® must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of PRANDIN®.

During maintenance programs, PRANDIN® should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations.

In considering the use of PRANDIN® or other antidiabetic therapies, it should be recognized that blood glucose control in type 2 diabetes has not been definitely established to be effective in preventing the long-term cardiovascular complications of diabetes. However, in patients with Type 1 diabetes, the Diabetes Control and Complications Trial (DCCT)

demonstrated that improved glycemic control, as reflected by HbA1C and fasting glucose levels, was associated with a reduction in the diabetic complications retinopathy, neuropathy, and nephropathy.

CONTRAINDICATIONS
PRANDIN® is contraindicated in patients with:
1. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
2. Type1 diabetes.
3. Known hypersensitivity to the drug or its inactive ingredients.

PRECAUTIONS
General: Hypoglycemia: All oral blood glucose-lowering drugs are capable of producing hypoglycemia. Proper patient selection, dosage, and instructions to the patients are important to avoid hypoglycemic episodes. Hepatic insufficiency may cause elevated repaglinide blood levels and may diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemia. Elderly, debilitated, or malnourished patients, and those with adrenal, pituitary, hepatic or severe renal insufficiency may be particularly susceptible to the hypoglycemic action of glucose-lowering drugs.

Hypoglycemia may be difficult to recognize in the elderly and in people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

The frequency of hypoglycemia is greater in patients with type 2 diabetes who have not been previously treated with oral blood glucose-lowering drugs (naive) or whose $HbA1_C$ is less than 8%. PRANDIN® should be administered with meals to lessen the risk of hypoglycemia.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of glycemic control may occur. At such times, it may be necessary to discontinue PRANDIN® and administer insulin. The effectiveness of any hypoglycemic drug in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when the drug is first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Information for Patients
Patients should be informed of the potential risks and advantages of PRANDIN® and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose and $HbA1_C$.The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development and concomitant administration of other glucose-lowering drugs should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Patients should be instructed to take PRANDIN® before meals (2, 3, or 4 times a day preprandially). Doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal. **Patients who skip a meal (or add an extra meal) should be instructed to skip (or add) a dose for that meal.**

Laboratory Tests
Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels with a goal of decreasing these levels towards the normal range. During dose adjustment, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Glycosylated hemoglobin may be especially useful for evaluating long-term glycemic control.

Drug Interactions
In vitro data indicate that repaglinide metabolism may be inhibited by antifungal agents like ketoconazole and miconazole, and antibacterial agents like erythromycin (cytochrome P-450 enzyme system 3A4 inhibitors). Drugs that induce the cytochrome P450 enzyme system 3A4 may increase repaglinide metabolism; such drugs include rifampin, barbiturates, and carbamezapine. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions**.

The hypoglycemic action of oral blood glucose-lowering agents may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When these drugs are administered to a patient receiving oral blood glucose-lowering agents, the patient should be observed for loss of glycemic control. When these drugs are withdrawn from a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for hypoglycemia.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term carcinogenicity studies were performed for 104 weeks at doses up to and including 120 mg/kg body weight/day (rats) and 500 mg/kg body weight/day (mice) or approximately 60 and 125 times clinical exposure, respectively, on a mg/m^2 basis. No evidence of carcinogenicity was found in mice or female rats. In male rats, there was an increased incidence of benign adenomas of the thyroid and liver. The relevance of these findings to humans is unclear. The no-effect doses for these observations in male rats were 30 mg/kg body weight/day for thyroid tumors and 60 mg/kg body weight/day for liver tumors, which are over 15 and 30 times, respectively, clinical exposure on a mg/m^2 basis.

Repaglinide was non-genotoxic in a battery of *in vivo* and *in vitro* studies: Bacterial mutagenesis (Ames test), *in vitro* forward cell mutation assay in V79 cells (HGPRT), *in vitro* chromosomal aberration assay in human lymphocytes, unscheduled and replicating DNA synthesis in rat liver, and *in vivo* mouse and rat micronucleus tests.

Fertility of male and female rats was unaffected by repaglinide administration at doses up to 80 mg/kg body weight/day (females) and 300 mg/kg body weight/day (males); over 40 times clinical exposure on a mg/m^2 basis.

Pregnancy
Pregnancy category C

Teratogenic Effects: Safety in pregnant women has not been established. Repaglinide was not teratogenic in rats or rabbits at doses 40 times (rats) and approximately 0.8 times (rabbit) clinical exposure (on a mg/m^2 basis) throughout pregnancy. Because animal reproduction studies are not always predictive of human response, PRANDIN® should be used during pregnancy only if it is clearly needed.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Offspring of rat dams exposed to repaglinide at 15 times clinical exposure on a mg/m^2 basis during days 17 to 22 of gestation and during lactation developed nonteratogenic skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. This effect was not seen at doses up to 2.5 times clinical exposure (on a mg/m^2 basis) on days 1 to 22 of pregnancy or at higher doses given during days 1 to 16 of pregnancy. Relevant human exposure has not occurred to date and therefore the safety of PRANDIN® administration throughout pregnancy or lactation cannot be established.

Nursing Mothers
In rat reproduction studies, measurable levels of repaglinide were detected in the breast milk of the dams and lowered blood glucose levels were observed in the pups. Cross fostering studies indicated that skeletal changes (see **Nonteratogenic Effects**) could be induced in control pups nursed by treated dams, although this occurred to a lesser degree than those pups treated *in utero*. Although it is not known whether repaglinide is excreted in human milk some oral agents are known to be excreted by this route. Because the potential for hypoglycemia in nursing infants may exist, and because of the effects on nursing animals, a decision should be made as to whether PRANDIN® should be discontinued in nursing mothers, or if mothers should discontinue nursing. If PRANDIN® is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use
No studies have been performed in pediatric patients.

Geriatric Use
In repaglinide clinical studies of 24 weeks or greater duration, 415 patients were over 65 years of age. In one-year, active-controlled trials, no differences were seen in effectiveness or adverse events between these subjects and those less than 65 other than the expected age-related increase in cardiovascular events observed for PRANDIN® and comparator drugs. There was no increase in frequency or severity of hypoglycemia in older subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals to PRANDIN® therapy cannot be ruled out.

ADVERSE REACTIONS
Hypoglycemia: See **Precautions** and **Overdosage** sections. PRANDIN® has been administered to 2931 individuals during clinical trials. Approximately 1500 of these individuals with type 2 diabetes have been treated for at least 3 months, 1000 for at least 6 months, and 800 for at least 1 year. The majority of these individuals (1228) received PRANDIN® in one of five 1-year, active-controlled trials. The comparator drugs in these 1-year trials were oral sulfonylurea drugs (SU) including glyburide and glipizide. Over one year, 13% of PRANDIN® patients were discontinued due to adverse events, as were 14% of SU patients. The most common adverse events leading to withdrawal were hyperglycemia, hypoglycemia, and related symptoms (see **PRECAUTIONS**). Mild or moderate hypoglycemia occurred in 16% of PRANDIN® patients, 20% of glyburide patients, and 19% of glipizide patients.

The table below lists common adverse events for PRANDIN® patients compared to both placebo (in trials 12 to 24 weeks duration) and to glyburide and glipizide in one year trials. The adverse event profile of PRANDIN® was generally comparable to that for sulfonylurea drugs (SU).

Commonly Reported Adverse Events (% of Patients)*

EVENT	PRANDIN® N = 352	PLACEBO N = 108	PRANDIN® N = 1228	SU N = 498
	Placebo controlled studies		Active controlled studies	
Metabolic				
Hypoglycemia	31**	7	16	20
Respiratory				
URI	16	8	10	10
Sinusitis	6	2	3	4
Rhinitis	3	3	7	8
Bronchitis	2	1	6	7
Gastrointestinal				
Nausea	5	5	3	2
Diarrhea	5	2	4	6
Constipation	3	2	2	3
Vomiting	3	3	2	1
Dyspepsia	2	2	4	2
Musculoskeletal				
Arthralgia	6	3	3	4
Back Pain	5	4	6	7
Other				
Headache	11	10	9	8
Paresthesia	3	3	2	1
Chest pain	3	1	2	1
Urinary tract infection	2	1	3	3
Tooth disorder	2	0	<1	<1
Allergy	2	0	1	<1

* Events ≥2% for the PRANDIN® group in the placebo-controlled studies and ≥ events in the placebo group

** See trial description in **CLINICAL PHARMACOLOGY, Clinical Trials**

Cardiovascular events also occur commonly in patients with type 2 diabetes. In one-year comparator trials, the incidence of individual events was not greater than 1% except for chest pain (1.8%) and angina (1.8%). The individual incidence of other cardiovascular events (hypertension, abnormal EKG, myocardial infarction, arrhythmias, and palpitations) was ≤1% and not different for PRANDIN® and the comparator drugs.

The incidence of serious cardiovascular adverse events added together, including ischemia, was slightly higher for repaglinide (4%) than for sulfonylurea drugs (3%) in controlled comparator clinical trials. In 1-year controlled trials, PRANDIN® treatment was not associated with excess mortality rates compared to rates observed with other oral hypoglycemic agent therapies.

Summary of Serious Cardiovascular Events (% of total patients with events)

	PRANDIN®	SU*
Total Exposed	1228	498
Serious CV Events	4%	3%
Cardiac Ischemic Events	2%	2%
Deaths due to CV Events	0.5%	0.4%

* glyburide and glipizide

Infrequent adverse events (<1% of patients)
Less common adverse clinical or laboratory events observed in clinical trials included elevated liver enzymes, thrombocytopenia, leukopenia, and anaphylactoid reactions (one patient).

Although no causal relationship has been established, postmarketing experience includes reports of the following rare adverse events: alopecia, hemolytic anemia, pancreatitis, Stevens-Johnson Syndrome, and severe hepatic dysfunction.

OVERDOSAGE
In a clinical trial, patients received increasing doses of PRANDIN® up to 80 mg a day for 14 days. There were few adverse effects other than those associated with the intended effect of lowering blood glucose. Hypoglycemia did not occur when meals were given with these high doses. Hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring may continue until the physician is assured that the patient is out of danger. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery. There is no evidence that repaglinide is dialyzable using hemodialysis.

Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid

intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL.

DOSAGE AND ADMINISTRATION
There is no fixed dosage regimen for the management of type 2 diabetes with PRANDIN®.

The patient's blood glucose should be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of an adequate blood glucose-lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels are of value in monitoring the patient's longer term response to therapy.

Short-term administration of PRANDIN® may be sufficient during periods of transient loss of control in patients usually well controlled on diet.

PRANDIN® doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal.

Starting Dose
For patients not previously treated or whose $HbA1_C$ is < 8%, the starting dose should be 0.5 mg with each meal. For patients previously treated with blood glucose-lowering drugs and whose $HbA1_C$ is $\geq$ 8%, the initial dose is 1 or 2 mg with each meal preprandially (see previous paragraph).

Dose Adjustment
Dosing adjustments should be determined by blood glucose response, usually fasting blood glucose. The preprandial dose should be doubled up to 4 mg with each meal until satisfactory blood glucose response is achieved. At least one week should elapse to assess response after each dose adjustment.

The recommended dose range is 0.5 mg to 4 mg taken with meals. PRANDIN® may be dosed preprandially 2, 3, or 4 times a day in response to changes in the patient's meal pattern. The maximum recommended daily dose is 16 mg.

Patient Management
Long-term efficacy should be monitored by measurement of $HbA1_c$ levels approximately every 3 months. Failure to follow an appropriate dosage regimen may precipitate hypoglycemia or hyperglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy including hypoglycemia.

Patients Receiving Other Oral Hypoglycemic Agents
When PRANDIN® is used to replace therapy with other oral hypoglycemic agents, PRANDIN® may be started on the day after the final dose is given. Patients should then be

observed carefully for hypoglycemia due to potential overlapping of drug effects. When transferred from longer half-life sulfonylurea agents (e.g., chlorpropamide) to repaglinide, close monitoring may be indicated for up to one week or longer.

Combination Therapy
If PRANDIN® monotherapy does not result in adequate glycemic control, metformin may be added. Or, if metformin therapy does not provide adequate control, PRANDIN® may be added. The starting dose and dose adjustments for PRANDIN® combination therapy is the same as for PRANDIN® monotherapy. The dose of each drug should be carefully adjusted to determine the minimal dose required to achieve the desired pharmacologic effect. Failure to do so could result in an increase in the incidence of hypoglycemic episodes. Appropriate monitoring of FPG and $HbA1_c$ measurements should be used to ensure that the patient is not subjected to excessive drug exposure or increased probability of secondary drug failure.

HOW SUPPLIED
PRANDIN® (repaglinide) tablets are supplied as unscored, biconvex tablets available in 0.5 mg (white), 1 mg (yellow) and 2 mg (peach) strengths. Tablets are embossed with the Novo Nordisk (Apis) bull symbol and colored to indicate strength.

0.5 mg tablets (white)	Bottles of 100	NDC 00169-0081-81
	Bottles of 500	NDC 00169-0081-82
	Bottles of 1000	NDC 00169-0081-83
1 mg tablets (yellow)	Bottles of 100	NDC 00169-0082-81
	Bottles of 500	NDC 00169-0082-82
	Bottles of 1000	NDC 00169-0082-83
2 mg tablets (peach)	Bottles of 100	NDC 00169-0084-81
	Bottles of 500	NDC 00169- 0084-82
	Bottles of 1000	NDC 00169-0084-83

Do not store above 25 C (77 F). Protect from moisture. Keep bottles tightly closed. Dispense in tight containers with safety closures.

Rx only.

PRANDIN® is a registered trademark of Novo Nordisk A/S.

Manufactured in Germany for
Novo Nordisk Pharmaceuticals, Inc.

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/s/

David Orloff

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