

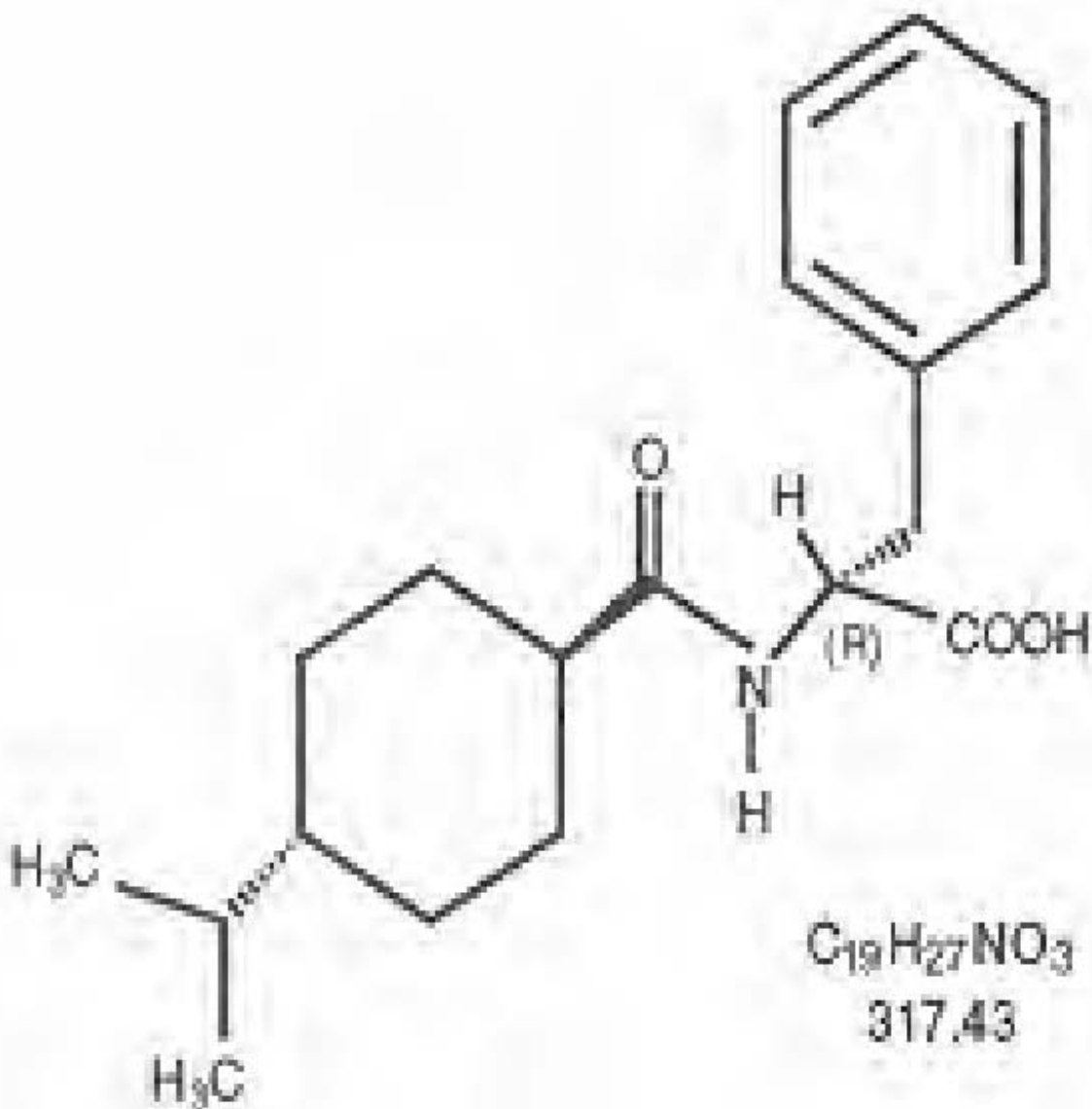
**NATEGLINIDE- nateglinide tablet, coated**  
**Par Pharmaceutical, Inc.**

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**Nateglinide tablet, coated**

**DESCRIPTION**

Nateglinide Tablets, USP are an oral antidiabetic agent used in the management of Type 2 diabetes mellitus [also known as non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes]. Nateglinide, (-)-N-[(trans-4-isopropylcyclohexane)carbonyl]-D-phenylalanine, is structurally unrelated to the oral sulfonylurea insulin secretagogues.

The structural formula is as shown



Nateglinide is a white powder with a molecular weight of 317.43. It is freely soluble in methanol,

ethanol, and chloroform, soluble in ether, sparingly soluble in acetonitrile and octanol, and practically insoluble in water. Nateglinide biconvex tablets contain 60 mg, or 120 mg, of nateglinide for oral administration.

**Inactive Ingredients:** colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch. The 60 mg also contains iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. In addition, the 120 mg contains FD&C Yellow #6/Sunset Yellow Aluminum Lake, iron oxide yellow.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Nateglinide is an amino-acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. This action is dependent upon functioning beta-cells in the pancreatic islets. Nateglinide interacts with the ATP-sensitive potassium ( $K^+_{ATP}$ ) channel on pancreatic beta-cells. The subsequent depolarization of the beta cell opens the calcium channel, producing calcium influx and insulin secretion. The extent of insulin release is glucose dependent and diminishes at low glucose levels. Nateglinide is highly tissue selective with low affinity for heart and skeletal muscle.

### Pharmacokinetics

#### Absorption

Following oral administration immediately prior to a meal, nateglinide is rapidly absorbed with mean peak plasma drug concentrations ( $C_{max}$ ) generally occurring within 1 hour ( $T_{max}$ ) after dosing. When administered to patients with Type 2 diabetes over the dosage range 60 mg to 240 mg three times a day for one week, nateglinide demonstrated linear pharmacokinetics for both AUC (area under the time/plasma concentration curve) and  $C_{max}$ .  $T_{max}$  was also found to be independent of dose in this patient population. Absolute bioavailability is estimated to be approximately 73%. When given with or after meals, the extent of nateglinide absorption (AUC) remains unaffected. However, there is a delay in the rate of absorption characterized by a decrease in  $C_{max}$  and a delay in time to peak plasma concentration ( $T_{max}$ ). Plasma profiles are characterized by multiple plasma concentration peaks when nateglinide is administered under fasting conditions. This effect is diminished when nateglinide is taken prior to a meal.

#### Distribution

Based on data following intravenous (IV) administration of nateglinide, the steady-state volume of distribution of nateglinide is estimated to be approximately 10 liters in healthy subjects. Nateglinide is extensively bound (98%) to serum proteins, primarily serum albumin, and to a lesser extent  $\alpha_1$  acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1 to 10 mcg/mL.

#### Metabolism

Nateglinide is metabolized by the mixed-function oxidase system prior to elimination. The major routes of metabolism are hydroxylation followed by glucuronide conjugation. The major metabolites are less potent antidiabetic agents than nateglinide. The isoprene minor metabolite possesses potency similar to that of the parent compound nateglinide.

*In vitro* data demonstrate that nateglinide is predominantly metabolized by cytochrome P450 isoenzymes CYP2C9 (70%) and CYP3A4 (30%).

#### Excretion

Nateglinide and its metabolites are rapidly and completely eliminated following oral administration.

Within 6 hours after dosing, approximately 75% of the administered <sup>14</sup>C-nateglinide was recovered in the urine. Eighty-three percent of the <sup>14</sup>C-nateglinide was excreted in the urine with an additional 10% eliminated in the feces. Approximately 16% of the <sup>14</sup>C-nateglinide was excreted in the urine as parent compound. In all studies of healthy volunteers and patients with Type 2 diabetes, nateglinide plasma concentrations declined rapidly with an average elimination half-life of approximately 1.5 hours. Consistent with this short elimination half-life, there was no apparent accumulation of nateglinide upon multiple dosing of up to 240 mg three times daily for 7 days.

## Drug Interactions

*In vitro* drug metabolism studies indicate that nateglinide is predominantly metabolized by the cytochrome P450 isozyme CYP2C9 (70%) and to a lesser extent CYP3A4 (30%). Nateglinide is a potential inhibitor of the CYP2C9 isoenzyme *in vivo* as indicated by its ability to inhibit the *in vitro* metabolism of tolbutamide. Inhibition of CYP3A4 metabolic reactions was not detected in *in vitro* experiments.

**Glyburide:** In a randomized, multiple-dose crossover study, patients with Type 2 diabetes were administered 120 mg nateglinide three times a day before meals for 1 day in combination with glyburide 10 mg daily. There were no clinically relevant alterations in the pharmacokinetics of either agent.

**Metformin:** When nateglinide 120 mg three times daily before meals was administered in combination with metformin 500 mg three times daily to patients with Type 2 diabetes, there were no clinically relevant changes in the pharmacokinetics of either agent.

**Digoxin:** When nateglinide 120 mg before meals was administered in combination with a single 1 mg dose of digoxin to healthy volunteers, there were no clinically relevant changes in the pharmacokinetics of either agent.

**Warfarin:** When healthy subjects were administered nateglinide 120 mg three times daily before meals for four days in combination with a single dose of warfarin 30 mg on day 2, there were no alterations in the pharmacokinetics of either agent. Prothrombin time was not affected.

**Diclofenac:** Administration of morning and lunch doses of nateglinide 120 mg in combination with a single 75 mg dose of diclofenac in healthy volunteers resulted in no significant changes to the pharmacokinetics of either agent.

## Special Populations

**Geriatric:** Age did not influence the pharmacokinetic properties of nateglinide. Therefore, no dose adjustments are necessary for elderly patients.

**Gender:** No clinically significant differences in nateglinide pharmacokinetics were observed between men and women. Therefore, no dose adjustment based on gender is necessary.

**Race:** Results of a population pharmacokinetic analysis including subjects of Caucasian, Black, and other ethnic origins suggest that race has little influence on the pharmacokinetics of nateglinide.

**Renal Impairment:** Compared to healthy matched subjects, patients with Type 2 diabetes and moderate-to-severe renal insufficiency (CrCl 15 to 50 mL/min) not on dialysis displayed similar apparent clearance, AUC and C<sub>max</sub>. Patients with Type 2 diabetes and renal failure on dialysis exhibited reduced overall drug exposure. However, hemodialysis patients also experienced reductions in plasma protein binding compared to the matched healthy volunteers.

**Hepatic Impairment:** The peak and total exposure of nateglinide in non-diabetic subjects with mild hepatic insufficiency were increased by 30% compared to matched healthy subjects. Nateglinide should be used with caution in patients with chronic liver disease. (See **PRECAUTIONS, Hepatic Impairment.**)

## Pharmacodynamics

Nateglinide is rapidly absorbed and stimulates pancreatic insulin secretion within 20 minutes of oral administration. When nateglinide is dosed three times daily before meals there is a rapid rise in plasma insulin, with peak levels approximately 1 hour after dosing and a fall to baseline by 4 hours after dosing.

In a double-blind, controlled clinical trial in which nateglinide was administered before each of three meals, plasma glucose levels were determined over a 12-hour, daytime period after 7 weeks of treatment. Nateglinide was administered 10 minutes before meals. The meals were based on standard diabetic weight maintenance menus with the total caloric content based on each subject's height. Nateglinide produced statistically significant decreases in fasting and postprandial glycemia compared to placebo.

## CLINICAL STUDIES

A total of 3,566 patients were randomized in nine double-blind, placebo-or active-controlled studies 8 to 24 weeks in duration to evaluate the safety and efficacy of nateglinide. 3,513 patients had efficacy values beyond baseline. In these studies nateglinide was administered up to 30 minutes before each of three main meals daily.

### Nateglinide Monotherapy Compared to Placebo

In a randomized, double-blind, placebo-controlled, 24-week study, patients with Type 2 diabetes with HbA1c  $\geq 6.8\%$  on diet alone were randomized to receive either nateglinide (60 mg or 120 mg three times daily before meals) or placebo. Baseline HbA1c ranged from 7.9% to 8.1% and 77.8% of patients were previously untreated with oral antidiabetic therapy. Patients previously treated with antidiabetic medications were required to discontinue that medication for at least 2 months before randomization. The addition of nateglinide before meals resulted in statistically significant reductions in mean HbA1c and mean fasting plasma glucose (FPG) compared to placebo (see Table 1). The reductions in HbA1c and FPG were similar for patients naïve to, and those previously exposed to, antidiabetic medications.

In this study, one episode of severe hypoglycemia (plasma glucose  $<36$  mg/dL) was reported in a patient treated with nateglinide 120 mg three times daily before meals. No patients experienced hypoglycemia that required third party assistance. Patients treated with nateglinide had statistically significant mean increases in weight compared to placebo (see Table 1).

In another randomized, double-blind, 24-week, active-and placebo-controlled study, patients with Type 2 diabetes were randomized to receive nateglinide (120 mg three times daily before meals), metformin 500 mg (three times daily), a combination of nateglinide 120 mg (three times daily before meals) and metformin 500 mg (three times daily), or placebo. Baseline HbA1c ranged from 8.3% to 8.4%. Fifty-seven percent of patients were previously untreated with oral antidiabetic therapy. Nateglinide monotherapy resulted in significant reductions in mean HbA1c and mean FPG compared to placebo that were similar to the results of the study reported above (see Table 2).

**Table 1: Endpoint results for a 24-week, fixed dose study of Nateglinide monotherapy**

	Placebo N=168	Nateglinide 60 mg three times daily before meals N=167	Nateglinide 120 mg three times daily before meals N=168
HbA1c (%)			
Baseline (mean) Change from baseline (mean) Difference from placebo (mean)	8.0 +0.2	7.9 -0.3 -0.5 <sup>a</sup>	8.1 -0.5 -0.7 <sup>a</sup>
FPG (mg/dL)	N=172	N=171	N=169
Baseline (mean) Change from baseline (mean) Difference from placebo (mean)	167.9 +9.1	161.0 +0.4 -8.7 <sup>a</sup>	166.5 -4.5 -13.6 <sup>a</sup>
<b>Weight (kg)</b>	<b>N=170</b>	<b>N=169</b>	<b>N=166</b>

Baseline (mean) Change from baseline (mean) Difference from placebo (mean)	85.8 - 0.7	83.7 +0.3 +1.0 <sup>a</sup>	86.3 +0.9 +1.6 <sup>a</sup>
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<sup>a</sup> p-value ≤0.004

## Nateglinide Monotherapy Compared to Other Oral Antidiabetic Agents

### *Glyburide*

In a 24-week, double-blind, active-controlled trial, patients with Type 2 diabetes who had been on a sulfonylurea for ≥ 3 months and who had a baseline HbA<sub>1c</sub> ≥6.5% were randomized to receive nateglinide (60 mg or 120 mg three times daily before meals) or glyburide 10 mg once daily. Patients randomized to nateglinide had significant increases in mean HbA<sub>1c</sub> and mean FPG at endpoint compared to patients randomized to glyburide.

### *Metformin*

In another randomized, double-blind, 24-week, active- and placebo-controlled study, patients with Type 2 diabetes were randomized to receive nateglinide (120 mg three times daily before meals), metformin 500 mg (three times daily), a combination of nateglinide 120 mg (three times daily before meals) and metformin 500 mg (three times daily), or placebo. Baseline HbA<sub>1c</sub> ranged from 8.3% to 8.4%. Fifty-seven percent of patients were previously untreated with oral antidiabetic therapy. Patients previously treated with antidiabetic medications were required to discontinue medication for at least 2 months before randomization. The reductions in mean HbA<sub>1c</sub> and mean FPG at endpoint with metformin monotherapy were significantly greater than the reductions in these variables with nateglinide monotherapy (see **Table 2**). Relative to placebo, nateglinide monotherapy was associated with significant increases in mean weight whereas metformin monotherapy was associated with significant decreases in mean weight. Among the subset of patients naïve to antidiabetic therapy, the reductions in mean HbA<sub>1c</sub> and mean FPG for nateglinide monotherapy were similar to those for metformin monotherapy (see **Table 2**). Among the subset of patients previously treated with other antidiabetic agents, primarily glyburide, HbA<sub>1c</sub> in the nateglinide monotherapy group increased slightly from baseline, whereas HbA<sub>1c</sub> was reduced in the metformin monotherapy group (see **Table 2**).

## Nateglinide Combination Therapy

### *Metformin*

In the active and placebo-controlled study of metformin and nateglinide described above, the combination of nateglinide and metformin resulted in statistically significantly greater reductions in HbA<sub>1c</sub> and FPG compared to either nateglinide or metformin monotherapy (see **Table 2**). Nateglinide, alone or in combination with metformin, significantly reduced the prandial glucose elevation from pre-meal to 2-hours post-meal compared to placebo and metformin alone.

In this study, one episode of severe hypoglycemia (plasma glucose ≤36 mg/dL) was reported in a patient receiving the combination of nateglinide and metformin and four episodes of severe hypoglycemia were reported in a single patient in the metformin treatment arm. No patient experienced an episode of hypoglycemia that required third party assistance. Compared to placebo, nateglinide monotherapy was associated with a statistically significant increase in weight, while no significant change in weight was observed with combined nateglinide and metformin therapy (see **Table 2**).

In another 24-week, double-blind, placebo-controlled trial, patients with Type 2 diabetes with HbA<sub>1c</sub> ≥6.8% after treatment with metformin (≥1500 mg daily for ≥1 month) were first entered into a four-week run-in period of metformin monotherapy (2000 mg daily) and then randomized to receive nateglinide (60 mg or 120 mg three times daily before meals) or placebo in addition to metformin. Combination therapy with nateglinide and metformin was associated with statistically significantly greater reductions in HbA<sub>1c</sub> compared to metformin monotherapy (-0.4% and -0.6% for nateglinide 60 mg and nateglinide

120 mg plus metformin, respectively).

**Table 2: Endpoint results for a 24-week study of Nateglinide monotherapy and combination with metformin**

	Placebo N=160	Nateglinide 120 mg three times daily before meals N=171	Metformin 500 mg three times daily N=172	Nateglinide 120 mg before meals plus Metformin* N=162
HbA <sub>1c</sub> (%) All				
Baseline (mean) Change from baseline (mean) Difference from placebo Naïve	8.3 +0.4 N=98	8.3 -0.4 <sup>bc</sup> -0.8 <sup>a</sup> N=99	8.4 -0.8 <sup>c</sup> -1.2 <sup>a</sup> N=98	8.4 -1.5 -1.9 <sup>a</sup> N=81
Baseline (mean) Change from baseline (mean) Difference from placebo Non-Naïve	8.2 +0.3 N=62	8.1 -0.7 <sup>c</sup> -1.0 <sup>a</sup> N=72	8.3 -0.8 <sup>c</sup> -1.1 <sup>a</sup> N=74	8.2 -1.6 -1.9 <sup>a</sup> N=81
Baseline (mean) Change from baseline (mean) Difference from placebo FPG (mg/dL) All	8.3 +0.6 N=166	8.5 +0.004 <sup>bc</sup> -0.6 <sup>a</sup> N=173	8.7 -0.8 <sup>c</sup> -1.4 <sup>a</sup> N=174	8.7 -1.4 -2.0 <sup>a</sup> N=167
Baseline (mean) Change from baseline (mean) Difference from placebo Weight (kg) All	194.0 +8.0 N=160	196.5 -13.1 <sup>bc</sup> -21.1 <sup>a</sup> N=169	196.0 -30.0 <sup>c</sup> - 38.0 <sup>a</sup> N=169	197.7 -44.9 -52.9 <sup>a</sup> N=160
Baseline (mean) Change from baseline (mean) Difference from placebo	85.0 - 0.4	85.0 +0.9 <sup>bc</sup> +1.3 <sup>a</sup>	86.0 -0.1 +0.3	87.4 +0.2 +0.6

a p-value ≤0.05 vs. placebo<sup>b</sup>

p-value ≤0.03 vs. metformin

c p-value ≤0.05 vs. combination

\* Metformin was administered three times daily

### ***Rosiglitazone***

A 24-week, double blind multicenter, placebo-controlled trial was performed in patients with Type 2 diabetes not adequately controlled after a therapeutic response to rosiglitazone monotherapy 8 mg daily. The addition of nateglinide (120 mg three times per day with meals) was associated with statistically significantly greater reductions in HbA<sub>1c</sub> compared to rosiglitazone monotherapy. The difference was -0.77% at 24 weeks. The mean change in weight from baseline was about +3 kg for patients treated with nateglinide plus rosiglitazone vs about +1 kg for patients treated with placebo plus rosiglitazone.

### ***Glyburide***

In a 12-week study of patients with Type 2 diabetes inadequately controlled on glyburide 10 mg once daily, the addition of nateglinide (60 mg or 120 mg three times daily before meals) did not produce any additional benefit.

## **INDICATIONS AND USAGE**

Nateglinide Tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus.

## **CONTRAINDICATIONS**

Nateglinide Tablets are contraindicated in patients with:

1. Known hypersensitivity to the drug or its inactive ingredients.
2. Type 1 diabetes.

3. Diabetic ketoacidosis. This condition should be treated with insulin.

## PRECAUTIONS

**Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with nateglinide or any other antidiabetic drug.

**Hypoglycemia:** All oral blood glucose lowering drugs that are absorbed systemically are capable of producing hypoglycemia. The frequency of hypoglycemia is related to the severity of the diabetes, the level of glycemic control, and other patient characteristics. Geriatric patients, malnourished patients, and those with adrenal or pituitary insufficiency or severe renal impairment are more susceptible to the glucose lowering effect of these treatments. The risk of hypoglycemia may be increased by strenuous physical exercise, ingestion of alcohol, insufficient caloric intake on an acute or chronic basis, or combinations with other oral antidiabetic agents. Hypoglycemia may be difficult to recognize in patients with autonomic neuropathy and/or those who use beta-blockers. Nateglinide should be administered prior to meals to reduce the risk of hypoglycemia. Patients who skip meals should also skip their scheduled dose of nateglinide to reduce the risk of hypoglycemia.

**Hepatic Impairment:** Nateglinide should be used with caution in patients with moderate-to-severe liver disease because such patients have not been studied.

### Loss of Glycemic Control

Transient loss of glycemic control may occur with fever, infection, trauma, or surgery. Insulin therapy may be needed instead of nateglinide therapy at such times. Secondary failure, or reduced effectiveness of nateglinide over a period of time, may occur.

### Information for Patients

Patients should be informed of the potential risks and benefits of nateglinide and of alternative modes of therapy. The risks and management of hypoglycemia should be explained. Patients should be instructed to take nateglinide 1 to 30 minutes before ingesting a meal, but to skip their scheduled dose if they skip the meal so that the risk of hypoglycemia will be reduced. Drug interactions should be discussed with patients. Patients should be informed of potential drug-drug interactions with nateglinide.

### Laboratory Tests

Response to therapies should be periodically assessed with glucose values and HbA<sub>1c</sub> levels.

### Drug Interactions

Nateglinide is highly bound to plasma proteins (98%), mainly albumin. *In vitro* displacement studies with highly protein-bound drugs such as furosemide, propranolol, captopril, nicardipine, pravastatin, glyburide, warfarin, phenytoin, acetylsalicylic acid, tolbutamide, and metformin showed no influence on the extent of nateglinide protein binding. Similarly, nateglinide had no influence on the serum protein binding of propranolol, glyburide, nicardipine, warfarin, phenytoin, acetylsalicylic acid and tolbutamide *in vitro*. However, prudent evaluation of individual cases is warranted in the clinical setting.

Certain drugs, including nonsteroidal anti-inflammatory agents (NSAIDs), salicylates, monoamine oxidase inhibitors, and non-selective beta-adrenergic-blocking agents, guanethidine, and CYP2C9 inhibitors (e.g., fluconazole, amiodarone, miconazole, oxandrolone) may potentiate the hypoglycemic action of nateglinide and other oral antidiabetic drugs.

Certain drugs including thiazides, corticosteroids, thyroid products, sympathomimetics, somatropin, rifampin, phenytoin and dietary supplements (St. John's wort) may reduce the hypoglycemic action of nateglinide and other oral antidiabetic drugs. Somatostatin analogues may potentiate or attenuate the hypoglycemic action of nateglinide.

When these drugs are administered to or withdrawn from patients receiving nateglinide, the patient

should be observed closely for changes in glycemic control.

### **Drug/Food Interactions**

The pharmacokinetics of nateglinide were not affected by the composition of a meal (high protein, fat, or carbohydrate). However, peak plasma levels were significantly reduced when nateglinide was administered 10 minutes prior to a liquid meal. Nateglinide did not have any effect on gastric emptying in healthy subjects as assessed by acetaminophen testing.

### **Carcinogenesis and Mutagenesis and Impairment of Fertility**

**Carcinogenicity:** A two-year carcinogenicity study in Sprague-Dawley rats was performed with oral doses of nateglinide up to 900 mg/kg/day, which produced AUC exposures in male and female rats approximately 30 and 40 times the human therapeutic exposure respectively with a recommended nateglinide dose of 120 mg, three times daily before meals. A two-year carcinogenicity study in B6C3F1 mice was performed with oral doses of nateglinide up to 400 mg/kg/day, which produced AUC exposures in male and female mice approximately 10 and 30 times the human therapeutic exposure with a recommended nateglinide dose of 120 mg, three times daily before meals. No evidence of a tumorigenic response was found in either rats or mice.

**Mutagenesis:** Nateglinide was not genotoxic in the *in vitro* Ames test, mouse lymphoma assay, chromosome aberration assay in Chinese hamster lung cells, or in the *in vivo* mouse micronucleus test.

**Impairment of Fertility:** Fertility was unaffected by administration of nateglinide to rats at doses up to 600 mg/kg (approximately 16 times the human therapeutic exposure with a recommended nateglinide dose of 120 mg three times daily before meals).

### **Pregnancy**

Pregnancy Category C:

Nateglinide was not teratogenic in rats at doses up to 1000 mg/kg (approximately 60 times the human therapeutic exposure with a recommended nateglinide dose of 120 mg, three times daily before meals). In the rabbit, embryonic development was adversely affected and the incidence of gallbladder agenesis or small gallbladder was increased at a dose of 500 mg/kg (approximately 40 times the human therapeutic exposure with a recommended nateglinide dose of 120 mg, three times daily before meals). There are no adequate and well controlled studies in pregnant women. Nateglinide should not be used during pregnancy.

### **Labor and Delivery**

The effect of nateglinide on labor and delivery in humans is not known.

### **Nursing Mothers**

Studies in lactating rats showed that nateglinide is excreted in the milk; the AUC<sub>0-48h</sub> ratio in milk to plasma was approximately 1:4. During the peri- and postnatal period body weights were lower in offspring of rats administered nateglinide at 1000 mg/kg (approximately 60 times the human therapeutic exposure with a recommended nateglinide dose of 120 mg, three times daily before meals). It is not known whether nateglinide is excreted in human milk. Because many drugs are excreted in human milk, nateglinide should not be administered to a nursing woman.

### **Pediatric Use**

Clinical trials to demonstrate the safety and effectiveness in pediatric patients have not been conducted.

### **Geriatric Use**

No differences were observed in safety or efficacy of nateglinide between patients age 65 and over,



and those under age 65. However, greater sensitivity of some older individuals to nateglinide therapy cannot be ruled out.

## ADVERSE REACTIONS

In clinical trials, approximately 2,600 patients with Type 2 diabetes were treated with nateglinide. Of these, approximately 1,335 patients were treated for 6 months or longer and approximately 190 patients for one year or longer.

Hypoglycemia was relatively uncommon in all treatment arms of the clinical trials. Only 0.3% of nateglinide patients discontinued due to hypoglycemia. Symptoms suggestive of hypoglycemia have been observed after administration of nateglinide. These symptoms included sweating, trembling, dizziness, increased appetite, palpitations, nausea, fatigue and weakness.

Gastrointestinal symptoms, especially diarrhea and nausea, were no more common in patients using the combination of nateglinide and metformin than in patients receiving metformin alone. Likewise, peripheral edema was no more common in patients using the combination of nateglinide and rosiglitazone than in patients receiving rosiglitazone alone. The following table lists events that occurred more frequently in nateglinide patients than placebo patients in controlled clinical trials.

### Common Adverse Events ( $\geq 2\%$ in nateglinide patients) in Nateglinide Monotherapy Trials (% of patients)

<b>Preferred Term</b>	<b>Placebo N=458</b>	<b>Nateglinide N=1441</b>
Upper Respiratory Infection	8.1	10.5
Back Pain	3.7	4.0
Flu Symptoms	2.6	3.6
Dizziness	2.2	3.6
Arthropathy	2.2	3.3
Diarrhea	3.1	3.2
Accidental Trauma	1.7	2.9
Bronchitis	2.6	2.7
Coughing	2.2	2.4
Hypoglycemia	0.4	2.4

During post-marketing experience, rare cases of hypersensitivity reactions such as rash, itching and urticaria have been reported. Similarly, cases of jaundice, cholestatic hepatitis and elevated liver enzymes have been reported.

### Laboratory Abnormalities

**Uric Acid:** There were increases in mean uric acid levels for patients treated with nateglinide alone, nateglinide in combination with metformin, metformin alone, and glyburide alone. The respective differences from placebo were 0.29 mg/dL, 0.45 mg/dL, 0.28 mg/dL, and 0.19 mg/dL. The clinical significance of these findings is unknown.

### OVERDOSAGE

In a clinical study in patients with Type 2 diabetes, nateglinide was administered in increasing doses up to 720 mg a day for 7 days and there were no clinically significant adverse events reported. There have been no instances of overdose with nateglinide in clinical trials. However, an overdose may result in an exaggerated glucose-lowering effect with the development of hypoglycemic symptoms. Hypoglycemic symptoms without loss of consciousness or neurological findings should be treated with oral glucose

and adjustments in dosage and/or meal patterns. Severe hypoglycemic reactions with coma, seizure, or other neurological symptoms should be treated with intravenous glucose. As nateglinide is highly protein bound, dialysis is not an efficient means of removing it from the blood.

## **DOSAGE AND ADMINISTRATION**

Nateglinide Tablets, USP should be taken 1 to 30 minutes prior to meals.

### **Monotherapy and Combination with Metformin or a Thiazolidinedione**

The recommended starting and maintenance dose of nateglinide, alone or in combination with metformin or a thiazolidinedione, is 120 mg three times daily before meals.

The 60 mg dose of nateglinide, either alone or in combination with metformin or a thiazolidinedione, may be used in patients who are near goal HbA<sub>1c</sub> when treatment is initiated.

### **Dosage in Geriatric Patients**

No special dose adjustments are usually necessary. However, greater sensitivity of some individuals to nateglinide therapy cannot be ruled out.

### **Dosage in Renal and Hepatic Impairment**

No dosage adjustment is necessary in patients with mild-to-severe renal insufficiency or in patients with mild hepatic insufficiency. Dosing of patients with moderate-to-severe hepatic dysfunction has not been studied. Therefore, nateglinide should be used with caution in patients with moderate-to-severe liver disease (see **PRECAUTIONS, Hepatic Impairment**).

## **HOW SUPPLIED**

Nateglinide Tablets, USP

60 mg

Pink color coated, round biconvex, beveled edge tablet debossed with “P 984” on one side and plain on the other side

Bottles of 100.....NDC 49884-984-01

Bottles of 500.....NDC 49884-984-05

Bottles of 1000.....NDC-49884-984-10

120 mg

Orange color coated, oval shaped biconvex, tablet debossed with “P 985” on one side and plain on the other side

Bottles of 100.....NDC 49884-985-01

Bottles of 500.....NDC 49884-985-05

Bottles of 1000.....NDC-49884-985-10

### **Storage**

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.]

Dispense in a tight, light resistant container.

Manufactured by:

**Par Pharmaceutical**

Chestnut Ridge, NY 10977

Revised: 02/2016

OS984-01-1-06

### PRINCIPAL DISPLAY PANEL – 60 MG, 100 TABLETS CONTAINER

NDC 49884-984-01

# Nateglinide Tablets, USP

## 60 mg

Rx only  
100 Tablets



**Each tablet contains:**  
Nateglinide, USP ..... 60 mg

**USUAL DOSAGE:**  
See accompanying prescribing information.

**KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.**

Dispense in a tight, light-resistant container as defined in the USP.

**Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]**

R06/18 LA984-01-1-05

Manufactured by:  
Par Pharmaceutical  
Chestnut Ridge, NY 10977



N 3 49884-984-014


### PRINCIPAL DISPLAY PANEL – 120 MG, 100 TABLETS CONTAINER

NDC 49884-985-01

# Nateglinide Tablets, USP

## 120 mg

Rx only  
100 Tablets



**Each tablet contains:**  
Nateglinide, USP ..... 120 mg

**USUAL DOSAGE:**  
See accompanying prescribing information.


**KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.**

Dispense in a tight, light-resistant container as defined in the USP.

**Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.]**

R06/18 LA985-01-1-05

Manufactured by:  
Par Pharmaceutical  
Chestnut Ridge, NY 10977



N 3 49884-985-011

## NATEGLINIDE

nateglinide tablet, coated

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:49884-984
Route of Administration	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NATEGLINIDE (UNII: 41X3PWK4O2) (NATEGLINIDE - UNII:41X3PWK4O2)	NATEGLINIDE	60 mg

## Inactive Ingredients

Ingredient Name	Strength
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONE (UNII: FZ989GH94E)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	

## Product Characteristics

Color	PINK	Score	no score
Shape	ROUND	Size	1mm
Flavor		Imprint Code	P;984
Contains			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49884-984-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	09/08/2009	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077463	09/08/2009	

## NATEGLINIDE

nateglinide tablet, coated

## Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:49884-985
Route of Administration	ORAL		

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NATEGLINIDE (UNII: 41X3PWK4O2) (NATEGLINIDE - UNII:41X3PWK4O2)	NATEGLINIDE	120 mg

## Inactive Ingredients

Ingredient Name	Strength
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONE (UNII: FZ989GH94E)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

## Product Characteristics

Color	ORANGE	Score	no score
Shape	OVAL	Size	6mm
Flavor		Imprint Code	P;985
Contains			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49884-985-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	09/08/2009	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077463	09/08/2009	

**Labeler** - Par Pharmaceutical, Inc. (092733690)

**Registrant** - Par Pharmaceutical Inc. (092733690)

Revised: 2/2019

Par Pharmaceutical, Inc.