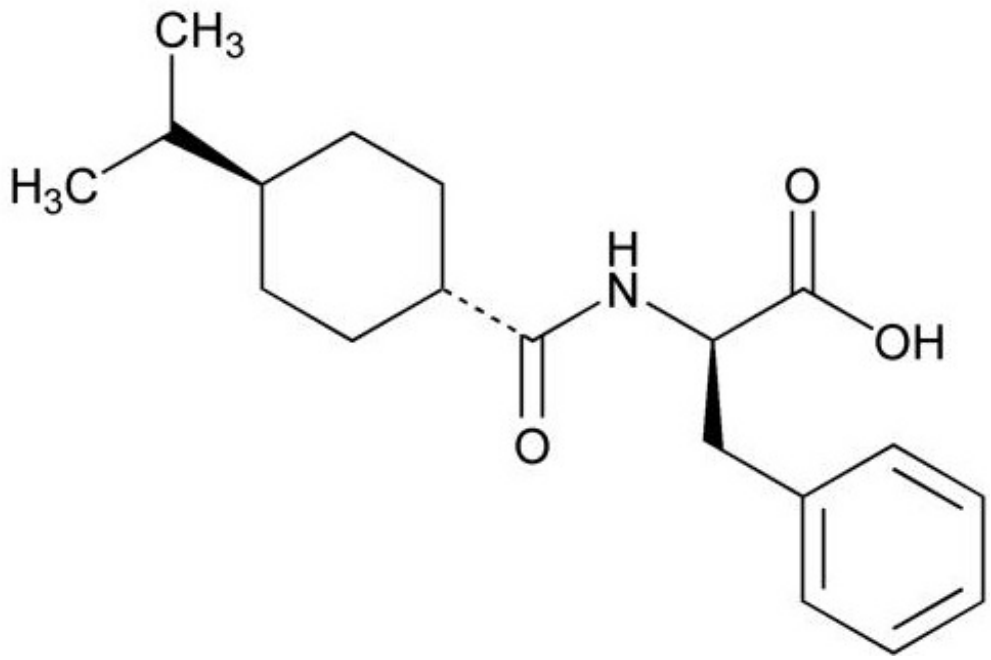
NATEGLINIDE- nateglinide tablet, film coated
ALVOGEN INC.

Nateglinide Tablets

DESCRIPTION

Nateglinide is 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 molecular formula is $C_{19}H_{27}NO_3$ and the structural formula is shown below:



Nateglinide, USP is a white powder with a molecular weight of 317.42. It is freely soluble in methanol, ethanol, and chloroform, soluble in ether, sparingly soluble in acetonitrile and octanol, and practically insoluble in water. Nateglinide tablets contain 60 mg or 120 mg of nateglinide for oral administration.

Inactive Ingredients: corn starch, lactose monohydrate, sodium starch glycolate, povidone, magnesium stearate, colloidal silicone dioxide, and crospovidone. The 60 mg tablet film coating contains hypromellose, titanium dioxide, polyethylene glycol, talc, and red iron oxide. The 120 mg tablet film coating contains hypromellose, titanium dioxide, polyethylene glycol, talc, and yellow iron oxide.

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 α1 acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1-10 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 ^{14}C-nateglinide was recovered in the urine. Eighty-three percent of the ^{14}C-nateglinide was excreted in the urine with an additional 10% eliminated in the feces. Approximately 16% of the ^{14}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 15-50 mL/min) not on dialysis displayed similar apparent clearance, AUC, and C_{max}. 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 $HbA_{1C} \geq 6.8\%$ on diet alone were randomized to receive either nateglinide (60 mg or 120 mg three times daily before meals) or placebo. Baseline HbA_{1C} 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 HbA_{1C} and mean fasting plasma glucose (FPG) compared to placebo (see Table 1). The reductions in HbA_{1C} 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 HbA_{1C} 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	Nateglinide 60 mg three times daily before meals	Nateglinide 120 mg three times daily before meals
HbA1C (%)	**N=168**	**N=167**	**N=169**
Baseline (mean)	8.0	7.9	8.1
Change from			

Change from baseline (mean)	+0.2	-0.3	-0.5
Difference from placebo (mean)		-0.5*	-0.7*
FPG (mg/dL)	**N=172**	**N=171**	**N=169**
Baseline (mean)	167.9	161.0	166.5
Change from baseline(mean)	+9.1	+0.4	-4.5
Difference from placebo (mean)		-8.7*	+13.6*
Weight (kg)	**N=170**	**N=169**	**N= 166**
Baseline (mean)	85.8	83.7	86.3
Change from baseline(mean)	-0.7	+0.3	+0.9
Difference from placebo (mean)		+1.0*	+1.6*

* 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_{1C} ≥ 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_{1C} 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_{1C} 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_{1C} 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_{1C} 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_{1C} in the nateglinide monotherapy group increased slightly from baseline, whereas HbA_{1C} 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_{1C} 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_{1C} ≥ 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_{1C} 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	**Nateglinide 120 mg three times daily before meals**	**Metformin 500 mg three times daily**	**Nateglinide 120 mg before meals plus Metformin***
HbA_{1C} (%)				
All	*N=160*	*N=171*	*N=172*	*N=162*
Baseline (mean)	8.3	8.3	8.4	8.4
Change from baseline (mean)	+0.4	-0.4 [bc]	-0.8 [c]	-1.5
Difference from placebo		-0.8 [a]	-1.2 [a]	-1.9 [a]
Naïve	*N=98*	*N=99*	*N=98*	*N=81*
Baseline (mean)	8.2	8.1	8.3	8.2
Change from baseline (mean)	+0.3	-0.7 [c]	-0.8 [c]	-1.6
Difference from placebo		-1.0 [a]	-1.1 [a]	-1.9 [a]

Non-Naïve	*N=62*	*N=72*	*N=74*	*N=81*
Baseline (mean)	8.3	8.5	8.7	8.7
Change from baseline (mean)	+0.6	+0.004 [bc]	-0.8 [c]	-1.4
Difference from placebo		-0.6 [a]	-1.4 [a]	-2.0 [a]
FPG (mg/dL)				
All	*N=166*	*N=173*	*N=174*	*N=167*
Baseline (mean)	194.0	196.5	196.0	197.7
Change from baseline (mean)	+8.0	-13.1 [bc]	-30.0 [c]	-44.9
Difference from placebo		-21.1 [a]	-38.0 [a]	-52.9 [a]
Weight (kg)				
All	*N=160*	*N=169*	*N=169*	*N=160*
Baseline (mean)	85.0	85.0	86.0	87.4
Change from baseline (mean)	-0.4	+0.9 [bc]	-0.1	+0.2
Difference from placebo		+1.3 a	+0.3	+0.6

a p-value ≤ 0.05 vs. placebo
b 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_{1C} 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 is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONTRAINDICATIONS

Nateglinide is 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_{1C} 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, phenytion and dietary supplements (St John's wort) may reduce the hypoglycemic 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, Mutagenesis, 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 $AUC_{0\text{-}48h}$ 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 (≥ 2% in Nateglinide patients) in Nateglinide Monotherapy Trials (% of patients)

	Placebo	Nateglinide
	N=458	N=1441
Preferred Term		
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 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_{1C} 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 and 120 mg are supplied as:

60 mg
Available as pink, round, film-coated tablet containing 60 mg nateglinide, debossed "ALG 233" on one side and plain on the other side.

Bottles of 30 NDC 47781-233-30
Bottles of 1000 NDC 47781-233-10

120 mg
Available as yellow, caplet shaped, film-coated tablet containing 120 mg nateglinide, debossed "ALG 234" on one side and plain on the other side.

Bottles of 30 NDC 47781-234-30
Bottles of 500 NDC 47781-234-05

Storage

Store at 20°- 25ºC (68°- 77ºF); excursions permitted to 15ºC-30ºC (59ºF-86ºF) [see USP Controlled Room Temperature.]

Dispense in a tight container, as defined in the USP.

Made in USA

Distributed by:
Alvogen, Inc.
Pine Brook, NJ 07058 USA

PI233-00
Rev. 04/2015

NDC 47781-**233**-30

NATEGLINIDE
TABLETS USP

60 mg

Rx only
30 Tablets

Alvogen®

NDC 47781-**23**4-30

NATEGLINIDE
TABLETS USP

120 mg

Rx only
30 Tablets

Alvogen®

NATEGLINIDE
nateglinide tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:47781-233
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**
STARCH, CORN (UNII: O8232NY3SJ)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
POVIDONE K30 (UNII: U725QWY32X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 68401960MK)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 4000 (UNII: 4R4HFI6D95)	
TALC (UNII: 7SEV7J4R1U)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics			
Color	PINK	**Score**	no score
Shape	ROUND	**Size**	10mm
Flavor		**Imprint Code**	ALV;233
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:47781-233-30	30 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:47781-233-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205055	12/22/2025	

NATEGLINIDE

nateglinide tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:47781-234

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
STARCH, CORN (UNII: O8232NY3SJ)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
POVIDONE K30 (UNII: U725QWY32X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 68401960MK)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 4000 (UNII: 4R4HFI6D95)	
TALC (UNII: 7SEV7J4R1U)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	

Product Characteristics

Color	YELLOW	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	ALV;234
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:47781-234-30	30 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:47781-234-05	500 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

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ANDA	ANDA205055	12/22/2025	

Labeler - ALVOGEN INC. (008057330)

Establishment

Name	Address	ID/FEI	Business Operations
Norwich Pharmaceuticals, Inc.		132218731	manufacture(47781-233, 47781-234) , analysis(47781-233, 47781-234) , pack(47781-233, 47781-234)

Revised: 11/2012 ALVOGEN INC.