NATEGLINIDE- nateglinide tablet
Dr. Reddy's Laboratories Limited

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NATEGLINIDE TABLETS safely and effectively. See full prescribing information for NATEGLINIDE TABLETS.
NATEGLINIDE tablets, for oral use
Initial U.S. Approval: 2000

INDICATIONS AND USAGE

Nateglinide is a glinide indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)
Limitations of Use: Not for treating type 1 diabetes mellitus or diabetes ketoacidosis (1)

DOSAGE AND ADMINISTRATION

- Recommended dose is 120 mg three times daily
- In patients who are near glycemic goal when treatment is initiated, 60 mg three times daily may be administered. (2)
- Administer 1 to 30 minutes before meals (2)
- If a meal is skipped, skip the scheduled dose to reduce the risk of hypoglycemia. (2, 5.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 60 mg and 120 mg (3)

CONTRAINDICATIONS

- History of hypersensitivity to nateglinide inactive ingredients (4)

WARNINGS AND PRECAUTIONS

- Hypoglycemia: Nateglinide may cause hypoglycemia. Administer before meals to reduce the risk of hypoglycemia. Skip the scheduled dose of nateglinide if a meal is skipped to reduce the risk of hypoglycemia. (5.1)
- Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with nateglinide. (5.2)

ADVERSE REACTIONS

- Common adverse reactions associated with nateglinide (3% or greater incidence) were upper respiratory tract infection, back pain, flu symptoms, dizziness, arthropathy, diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Dr. Reddy's Laboratories Inc., at 1-888-375-3784 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs That May Increase the Potential for Hypoglycemia: Nateglinide dose reductions and increased frequency of glucose monitoring may be required when co-administered (7)
- Drugs That May Increase the Potential for Hyperglycemia: Nateglinide dose increases and increased frequency of glucose monitoring may be required when co-administered (7)
- Drugs That May Blunt Signs and Symptoms of Hypoglycemia: Increased frequency of glucose monitoring may be required when co-administered (7)

USE IN SPECIFIC POPULATIONS

- Lactation: Nateglinide is not recommended when breastfeeding (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 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.

Limitations of Use: Nateglinide tablets should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

2 DOSAGE AND ADMINISTRATION

The recommended dose of nateglinide tablets is 120 mg orally three times daily before meals.

The recommended dose of nateglinide tablets is 60 mg orally three times daily before meals in patients who are near glycemic goal when treatment is initiated.

Instruct patients to take nateglinide tablets 1 to 30 minutes before meals.

In patients who skip meals, instruct patients to skip the scheduled dose of nateglinide tablets to reduce the risk of hypoglycemia [see Warnings and Precautions (5.1)].

3 DOSAGE FORMS AND STRENGTHS

- 60 mg tablets: white to off-white, round, biconvex tablets embossed with ‘RDY’ on one side and ‘328’ on other side.
- 120 mg tablets: white to off-white, round, biconvex tablets embossed with ‘RDY’ on one side and ‘329’ on other side.

4 CONTRAINDICATIONS

Nateglinide is contraindicated in patients with a history of hypersensitivity to nateglinide tablets or its inactive ingredients.

5 WARNINGS AND PRECAUTIONS

5.1 Hypoglycemia

All glinides, including nateglinide, can cause hypoglycemia [see Adverse Reactions (6.1**)**]. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery).

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic neuropathy (nerve disease), in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) [see Drug Interactions (7)], or in patients who experience recurrent hypoglycemia.

Factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content), changes in level of physical activity, changes to coadministered medication [see Drug Interactions (7)**],** and concomitant use with other antidiabetic agents. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see Use in Specific Populations (8.6,8.7), Clinical Pharmacology (12.3)].

Patients should take nateglinide before meals and be instructed to skip the dose of nateglinide if a meal is skipped [see Dosage and Administration (2)]. Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have

reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.2 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with nateglinide.

6 ADVERSE REACTIONS

The following serious adverse reaction is also described elsewhere in the labeling:

- Hypoglycemia [see Warnings and Precautions (5.1)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, approximately 2,600 patients with type 2 diabetes mellitus 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. Table 1 shows the most common adverse reactions associated with nateglinide.

Table 1: Adverse Reactions other than Hypoglycemia (%) occurring Greater than or equal to 2% in Nateglinide-Treated Patients from Pool of 12 to 64 week Placebo Controlled Trials

	Placebo N=458	**Nateglinide** N=1441
Preferred Term		
Upper Respiratory Infection	8.1	10.5
Back Pain	3.7	4
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

Episodes of severe hypoglycemia (plasma glucose less than 36 mg/dL) were reported in two patients treated with nateglinide. Non-severe hypoglycemia occurred in 2.4 % of nateglinide treated patients and 0.4 % of placebo treated patients [see Warnings and Precautions (5.1)].

Weight Gain

Patients treated with nateglinide had statistically significant mean increases in weight

compared to placebo. In clinical trials, the mean weight increases with nateglinide 60 mg (3 times daily) and nateglinide 120 mg (3 times daily) compared to placebo were 1 kg and 1.6 kg respectively.

Laboratory Test

Increases in 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of nateglinide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity Reactions: Rash, itching, and urticaria
- Hepatobiliary Disorders: Jaundice, cholestatic hepatitis, and elevated liver enzymes

7 DRUG INTERACTIONS

Table 2 includes a list of drugs with clinically important drug interactions when concomitantly administered or withdrawn with nateglinide and instructions for managing or preventing them.

Table 2: Clinically Significant Drug Interactions with Nateglinide

Drugs That May Increase the Blood-Glucose-Lowering Effect of Nateglinide and Susceptibility to Hypoglycemia	
Drugs:	Nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, monoamine oxidase inhibitors, non-selective beta-adrenergic-blocking agents, anabolic hormones (e.g. methandrostenolone), guanethidine, gymnema sylvestre, glucomannan, thioctic acid, and inhibitors of CYP2C9 (e.g. amiodarone, fluconazole, voriconazole, sulfinpyrazone), or in patients known to be poor metabolizers of CYP2C9 substrates, alcohol.
Intervention:	Dose reductions and increased frequency of glucose monitoring may be required when nateglinide is coadministered with these drugs.
Drugs and Herbals That May Reduce the Blood-Glucose-Lowering Effect of Nateglinide and Increase Susceptibility to	

Hyperglycemia	
Drugs:	Thiazides, corticosteroids, thyroid products, sympathomimetics, somatropin, somatostatin analogues (e.g. lanreotide, octreotide), and CYP inducers (e.g. rifampin, phenytoin and St John's Wort).
Intervention:	Dose increases and increased frequency of glucose monitoring may be required when nateglinide is coadministered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
Drugs:	beta-blockers, clonidine, guanethidine, and reserpine
Intervention:	Increased frequency of glucose monitoring may be required when nateglinide is coadministered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The available data from published literature and the applicant's pharmacovigilance with use of nateglinide in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*. Nateglinide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In animal reproduction studies, there was no teratogenicity in rats and rabbits administered oral nateglinide during organogenesis at approximately 27 and 8 times the maximum recommended human dose (MRHD), respectively, based on body surface area (BSA).

The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a HbA1c > 7 and has been reported to be as high as 20% to 25% in women with a HbA1c > 10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal data

In embryofetal development studies, nateglinide administered orally during the period of

organogenesis was not teratogenic in rats at doses up to 1,000 mg/kg (corresponding to 27 times the MRHD of 120 mg three times per day, based on BSA). In rabbits, embryonic development was adversely affected at 500 mg/kg/day and the incidence of gallbladder agenesis or small gallbladder was increased at a dose of 300 and 500 mg/kg (corresponding to 16 and 27 times the MRHD). No such effects were observed at 150 mg/kg/day (corresponding to 8 times the MRHD). In a pre-and postnatal development study in rats, nateglinide administered by oral gavage at doses of 100, 300, and 1000 mg/kg/day from gestation day 17 to lactation day 21 resulted in lower body weight in offspring of rats administered nateglinide at 1,000 mg/kg/day (corresponding to 27 times the MHRD).

8.2 Lactation

Risk summary

There are no data on the presence of nateglinide in human milk, the effects on the breastfeeding infant, or the effects on milk production. The drug is present in animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk (see Data). Because the potential for hypoglycemia in breast-fed infants, advise women that use of nateglinide is not recommended while breastfeeding.

Data

In rat reproduction studies, nateglinide and its metabolite are excreted in the milk following oral dose (300 mg/kg). The overall milk: plasma (M/P) concentration ratio of the total radioactivity was approximately 1.4 based on AUC0-48 values. The M/P ratio of unchanged nateglinide was approximately 2.2.

8.4 Pediatric Use

The safety and effectiveness of nateglinide have not been established in pediatric patients.

8.5 Geriatric Use

436 patients 65 years and older, and 80 patients 75 years and older were exposed to nateglinide in clinical studies. 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.

8.6 Renal Impairment

No dosage adjustment is recommended in patients with mild to severe renal impairment [see **Clinical Pharmacology (**12.3**)**].

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment. Use of nateglinide in patients with moderate-to-severe hepatic impairment has not been studied and therefore, should be used with caution in these patients [see **Clinical Pharmacology (**12.3**)**].

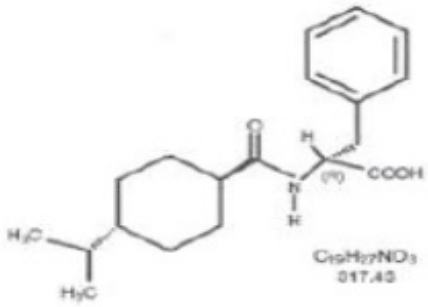
10 OVERDOSAGE

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.

11 DESCRIPTION

Nateglinide is an oral blood glucose-lowering drug of the glinide class. 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 an off-white to white powder with a molecular weight of 317.43 g/mol. 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: carnauba wax, copovidone, croscarmellose sodium, mannitol, silicon dioxide, sodium lauryl sulfate, sodium stearyl fumarate, corn starch and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nateglinide 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.

12.2 Pharmacodynamics

Nateglinide stimulates pancreatic insulin secretion within 20 minutes of oral

administration. When nateglinide is dosed before meals, the peak rise in plasma insulin occurs approximately 1 hour after dosing and falls to baseline by 4 hours after dosing.

12.3 Pharmacokinetics

In patients with Type 2 diabetes, multiple dose administration of nateglinide over the dosage range of 60 mg to 240 mg shows linear pharmacokinetics for both area under the curve (AUC) and C_{max}. In patients with Type 2 diabetes, there is no apparent accumulation of nateglinide upon multiple dosing of up to 240 mg three times daily for 7 days.

Absorption

Absolute bioavailability of nateglinide is approximately 73%. 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. Following oral administration immediately prior to a meal, the mean peak plasma nateglinide concentrations (C_{max}) generally occur within 1 hour (T_{max}) after dosing. T_{max} is independent of dose.

The pharmacokinetics of nateglinide are not affected by the composition of a meal (high protein, fat, or carbohydrate). However, peak plasma levels are significantly reduced when nateglinide is administered 10 minutes prior to a liquid meal as compared to solid meal. 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}).

Nateglinide did not have any effect on gastric emptying in healthy subjects as assessed by acetaminophen testing.

Distribution

Following intravenous (IV) administration of nateglinide, the steady-state volume of distribution of nateglinide is estimated to be approximately 10 L 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 to 10 mcg/mL.

Elimination

In healthy volunteers and patients with type 2 diabetes mellitus, nateglinide plasma concentrations declined with an average elimination half-life of approximately 1.5 hours.

Metabolism

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%).

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.

Excretion

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

Specific Populations

Renal Impairment No pharmacokinetic data are available in subjects with mild renal impairment (CrCl 60 to 89 mL/min). Compared to healthy matched subjects, patients with type 2 diabetes mellitus and moderate and severe renal impairment (CrCl 15 to 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 (C_{max} decreased by 49%; not statistically significant). However, hemodialysis patients also experienced reductions in plasma protein binding compared to the matched healthy volunteers.

In a cohort of 8 patients with type 2 diabetes and end-stage renal disease (ESRD) (eGFR < 15 mL/min/1.73m^2) M1 metabolite accumulation up to 1.2 ng/mL occurred with a dosage of 90 mg once daily for 1 to 3 months. In another cohort of 8 patients with type 2 diabetes on hemodialysis, M1 concentration decreased after a single session of hemodialysis. Although the hypoglycemic activity of the M1 metabolite is approximately 5 times lower than nateglinide, metabolite accumulation may increase the hypoglycemic effect of the administered dose.

Hepatic Impairment

In patients with mild hepatic impairment, the mean increase in C_{max} and AUC of nateglinide were 37% and 30 % respectively, as compared to healthy matched control subjects. There is no data on pharmacokinetics of nateglinide in patients with moderate-to-severe hepatic impairment.

Gender

No clinically significant differences in nateglinide pharmacokinetics were observed between men and women.

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.

Age

Age does not influence the pharmacokinetic properties of nateglinide.

Drug Interactions:

***In vitro* assessment of drug interactions**

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.

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.

***In vivo*assessment of drug interactions** The effect of coadministered drugs on the pharmacokinetics of nateglinide and the effect of nateglinide on pharmacokinetics of coadministered drugs are shown in Tables 3 and 4. No clinically relevant change in pharmacokinetic parameters of either agent was reported when nateglinide was coadministered with glyburide, metformin, digoxin, warfarin, and diclofenac.

Table 3: Effect of Coadministered Drugs on Pharmacokinetics of Nateglinide

Coadministered drug	Dosing regimen of coadministered drug	Dosing regimen of nateglinide	Change in Cmax	Change in AUC
Glyburide	10 mg once daily for 3 weeks	120 mg three times a day, single dose	8.78% ↓	3.53 % ↓
Metformin	500 mg three times a day for 3 weeks	120 mg three times a day, single dose	AM: 7.14% ↑ PM: 11.4% ↓	AM: 1.51% ↑ PM: 5.97% ↑
Digoxin	1 mg, single dose	120 mg three times a day, single dose	AM: 2.17% ↓ PM: 3.19% ↑	AM: 7.62% ↑ PM: 2.22% ↑
Warfarin	30 mg, single dose	120 mg three times a day for 4 days	2.65% ↑	3.72% ↓
Diclofenac	75 mg, single dose	120 mg twice daily, single dose dose	AM: 13.23% ↓ *PM: 3.76% ↑	AM: 2.2% ↓ *PM: 7.5% ↑

AM: after morning dose; PM: after evening dose; * after second dose; ↑: increase in the parameter; ↓: decrease in the parameter

Table 4: Effect of Nateglinide on Pharmacokinetics of Coadministered Drugs

Coadministered drug	Dosing regimen of coadministered drug	Dosing regimen of nateglinide	Change in C_{max}	Change in AUC
Glyburide	10 mg once daily for 3 weeks	120 mg three times a day, single dose	3.18% ↓	7.34% ↓
Metformin	500 mg three times a day for 3 weeks	120 mg three times a day, single dose	AM: 10.7% ↑ PM: 0.40% ↑	AM:13.3% ↑ PM: 2.27% ↓
Digoxin	1 mg, single dose	120 mg three times a day, single dose	5.41% ↓	6.58 % ↑
Warfarin	30 mg, single dose	120 mg three times a day for	R-warfarin: 1.03% ↓ S-	R-warfarin: 0.74% ↑ S-

Warfarin	30 mg, single dose	times a day for 4 days	warfarin: 0.85% ↓	warfarin: 7.23% ↑
Diclofenac	75 mg, single dose	120 mg twice daily, single dose	2.19% ↑	7.97% ↑

AM: after morning dose; PM: after evening dose; SD: single dose; ↑: increase in the parameter; ↓: decrease in the parameter

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity: Nateglinide did not increase tumors in two year carcinogenicity studies conducted in mice and rats. Oral doses of nateglinide up to 900 mg/kg in rats and 400 mg/kg in mice were tested, which produced exposures in rats approximately 30 to 40 times and in mice 10 to 30 times the human therapeutic exposure of nateglinide at a dose of 120 mg three times daily, based on AUC.

Mutagenesis: Nateglinide was not genotoxic in the in vitro Ames test, mouse lymphoma assay, chromosome aberration assay 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 (corresponding to 16 times the MRHD of 120 mg three times per day, based on BSA).).

14 CLINICAL STUDIES

14.1 Monotherapy

In a 24-week, double-blind, placebo-controlled study, patients with type 2 diabetes were randomized to receive either nateglinide (60 mg or 120 mg three times daily before meals) or placebo. Patients previously treated with antidiabetic medications were required to discontinue that medication for at least 2 months before randomization.

At Week 24, treatment with nateglinide before meals resulted in statistically significant reductions in mean HbA_{1C} and mean fasting plasma glucose (FPG) compared to placebo (see Table 5). The reductions in HbA_{1C} and FPG were similar for patient's naïve to, and those previously exposed to, antidiabetic medications.

Table 5: Endpoint Results for a 24-Week, Fixed Dose Study of Nateglinide Monotherapy

HbA_{1C} (%)	**Placebo** *N=168*	**Nateglinide 60 mgthree timesdailybefore meals** *N=167*	**Nateglinide 120 mgthree timesdailybefore meals** *N=168*
Baseline (mean)	8	7.9	8.1
Change from			

baseline (mean)	+0.2	-0.3	-0.5
Difference from placebo (mean)		-0.5 [a]	-0.7 [a]
FPG (mg/dL)	*N=172*	*N=171*	*N=169*
Baseline (mean)	167.9	161	166.5
Change from baseline (mean)	+9.1	+0.4	-4.5
Difference from placebo (mean)		-8.7[a]	-13.6[a]

[a] p-value ≤ 0.004

14.2 Monotherapy Compared to Glyburide

In a 24-week, double-blind, active-controlled trial, patients with type 2 diabetes who had been on a sulfonylurea for 3 or more months and who had a baseline HbA_{1C} greater than or equal to 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 statistically significant increases in mean HbA_{1C} and mean FPG at endpoint compared to patients randomized to glyburide.

Table 6: Endpoint Results for a 24-week Study of Nateglinide Monotherapy Compared to Glyburide

	Glyburide 10 mg Once daily	**Nateglinide 60 mg three times dailybefore meals**	**Nateglinide 120 mg three times dailybefore meals**
HbA_{1C} (%)	*N=183*	*N=178*	*N=179*
Baseline (mean)	7.8	8	7.9
Change from baseline (mean)	0.3	1.3	1.1
Difference from glyburide		1[a]	0.9[a]
FPG (mmol/L)	*N=184*	*N=182*	*N=180*
Baseline (mean)	9.44	9.67	9.61

Change from baseline (mean)	0.19	3.06	2.84
Difference from glyburide		2.87[a]	2.66[a]

[a] p-value <0.001

14.3 Monotherapy and In Combination With Metformin

In a 24-week, double-blind, active- and placebo-controlled study, patients with type 2 diabetes were randomized to receive either nateglinide alone (120 mg three times daily before meals), metformin alone (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. 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.

At Week 24, statistically significant reductions in mean HbA_{1c} and FPG were observed with metformin monotherapy compared to nateglinide monotherapy, and the combination of nateglinide and metformin compared to either nateglinide or metformin monotherapy (see Table 7).

Compared to placebo, nateglinide monotherapy was associated with a statistically significant increase in mean body weight, while no significant change in body weight was observed with metformin monotherapy or combination of nateglinide and metformin therapy (see Table 7). 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 7).

Table 7: Endpoint Results for a 24-Week study of Nateglinide Monotherapy and Combination with Metformin

	Placebo	**Nateglinide 120 mgthree timesdaily beforemeals**	**Metformin500 mgthree timesdaily**	**Nateglinide 120 mgbeforemeals plusMetformin***
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	+0.3	-0.7[c]	-0.8[c]	-1.6

(mean)	+0.3	-0.7 [c]	-0.8 [c]	-1.6
Difference from placebo		-1[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) Difference from placebo	+0.6	+0.004 [bc] -0.6[a]	-0.8 [c] -1.4[a]	-1.4 -2[a]
FPG (mg/dL) All	*N=166*	*N=173*	*N=174*	*N=167*
Baseline (mean)	1940	196.5	196	197.7
Change from baseline (mean) Difference from placebo	+8	-13.1[bc] -21.1[a]	-30[c] -38[a]	-44.9 -52.9[a]

[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

In another 24-week, double-blind, placebo-controlled trial, patients with type 2 diabetes with HbA_{1C} greater than or equal to 6.8% after treatment with metformin (greater than or equal to 1500 mg daily for at least 1 month) were first entered into a four week run-in period of metformin monotherapy (2000 mg daily) and then randomized to receive either nateglinide (60 mg or 120 mg three times daily before meals) or placebo as add-on to metformin. At the end of treatment, nateglinide 60 mg and 120 mg three times daily resulted in a statistically significantly greater reductions in HbA_{1C} compared to placebo when added to metformin (-0.4% and -0.6% for nateglinide 60 mg and nateglinide 120 mg plus metformin, respectively).

Table 8: Endpoint Results for a 24-week Study of Nateglinide Monotherapy as Add-on to Metformin

	Placebo+metformin	**Nateglinide 60 mg+metformin**	**Nateglinide 120 mg+ metformin**
HbA_{1C} (%)	N=150	N=152	N=154
Baseline (mean)	8.2	8	8.2
Change from baseline (mean)	0.01	-0.4	-0.6
Difference from metformin		-0.4[a]	-0.6[b]

[a] p-value 0.003 vs. metformin

[b] p-value < 0.001 vs. metformin

All nateglinide/placebo taken three times daily before meals; all metformin 1000 mg twice daily.

14.4 Add-On Combination Therapy With Rosiglitazone

A 24-week, double blind, multicenter, placebo-controlled trial was performed in patients with type 2 diabetes not adequately controlled on rosiglitazone 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 placebo as add-on to rosiglitazone. The mean change in weight from baseline was +3 kg for patients treated with nateglinide compared to +1 kg for patients treated with placebo when added to rosiglitazone.

Table 9: Endpoint Results for a 24-week Study of the Effect of Adding Nateglinide or Placebo to Rosiglitazone

	Placebo +rosiglitazone8 mgonce daily	**Nateglinide 120 mgbefore meals +rosiglitazone8 mgonce daily**
HbA_{1C} (%)	*N=191*	*N=194*
Baseline (mean)	8.4	8.3
Change from baseline (mean)	0.03	-0.7
Difference from rosiglitazone (mean)		-0.7[a]

[a] p-value ≤ 0.0001

14.5 Add-On Combination Therapy With 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.

Table 10: Endpoint Results for a 12-week Study of the Effect of Adding Nateglinide or Placebo to Glyburide

	Placebo +glyburide10 mg once daily	**Nateglinide 60 mgbefore meals + glyburide10 mg once daily**	**Nateglinide 120 mgbefore meals + glyburide 10 mgonce daily**
HbA_{1C} (%)	N=58	N=55	N=54
Baseline (mean)	8.7	8.7	8.7
Change from baseline (mean)	0.3	0.2	-0.02

Difference from glyburide (mean)		-0.1[a]	-0.3[b]

Placebo or nateglinide given 10 minutes prior to breakfast, lunch, and dinner; glyburide given with the breakfast dose of nateglinide or placebo.

[a] p-value 0.6959

[b] p-value 0.1246

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Nateglinide tablets USP are available as 60 mg white to off-white, round, biconvex tablets embossed with ‘RDY’ on one side and ‘328’ on other side and they are supplied in bottles of 30, 90, 100, 500 and unit dose package of 100 (10 x 10).

Bottles of 30 NDC 55111-328-30

Bottles of 90 NDC 55111-328-90

Bottles of 100 NDC 55111-328-01

Bottles of 500 NDC 55111-328-05

Unit dose package of 100 (10 x 10) NDC 55111-328-78

Nateglinide tablets USP are available as 120 mg white to off-white, round, biconvex tablets embossed with ‘RDY’ on one side and ‘329’ on other side and they are supplied in bottles of 30, 90, 100, 500 and unit dose package of 100 (10 x 10).

Bottles of 30 NDC 55111-329-30

Bottles of 90 NDC 55111-329-90

Bottles of 100 NDC 55111-329-01

Bottles of 500 NDC 55111-329-05

Unit dose package of 100 (10 x 10) NDC 55111-329-78

Storage and Handling

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

Dispense in a tight container, USP.

17 PATIENT COUNSELING INFORMATION

Administration

Instruct patients to take nateglinide 1 to 30 minutes before meals. Instruct patients that skip meals to skip their dose of nateglinide [see **Dosage and Administration (2)**].

Hypoglycemia

Inform patients that nateglinide can cause hypoglycemia and instruct patients and their caregivers on self-management procedures including glucose monitoring and management of hypoglycemia. Inform patients that their ability to concentrate and react may be impaired as a result of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended [see **Warnings and Precautions (5.1)**].

Lactation

Advise patients that use of nateglinide is not recommended while breastfeeding [see **Use in Specific Populations (8.2)**].

Drug Interactions

Discuss potential drug interactions with patients and inform them of potential drug-drug interactions with nateglinide.

Rx only

Manufactured by:

Dr. Reddy's Laboratories Limited

Bachupally – 500 090 INDIA

Revised: 1121

PACKAGE LABEL PRINCIPAL DISPLAY PANEL SECTION

Nateglinide Tablets USP, 60 mg - Container Label

Unvarnished Area consists of: 2D Bar code, Lot Number, Expiry Date and Serial Number.

Nateglinide Tablets USP, 60 mg - Carton Label

Nateglinide Tablets USP, 120 mg - Container Label

Nateglinide Tablets USP, 120 mg - Carton Label

NATEGLINIDE

nateglinide tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:55111-328
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**
carnauba wax (UNII: R12CBM0EIZ)	
copovidone (UNII: D9C330MD8B)	
croscarmellose sodium (UNII: M28OL1HH48)	

mannitol (UNII: 3OWL53L36A)	
silicon dioxide (UNII: ETJ7Z6XBU4)	
sodium lauryl sulfate (UNII: 368GB5141J)	
sodium stearyl fumarate (UNII: 7CV7WJK4UI)	
starch, corn (UNII: O8232NY3SJ)	
talc (UNII: 7SEV7J4R1U)	

Product Characteristics

Color	WHITE (white to off white)	**Score**	no score
Shape	ROUND (biconvex)	**Size**	9mm
Flavor		**Imprint Code**	RDY;328
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55111-328-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	09/09/2009	
2	NDC:55111-328-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	09/09/2009	
3	NDC:55111-328-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/09/2009	
4	NDC:55111-328-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	09/09/2009	
5	NDC:55111-328-78	10 in 1 CARTON	09/09/2009	
5	NDC:55111-328-79	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077461	09/09/2009	

NATEGLINIDE

nateglinide tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:55111-329
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
carnauba wax (UNII: R12CBM0EIZ)	
copovidone (UNII: D9C330MD8B)	
croscarmellose sodium (UNII: M28OL1HH48)	
mannitol (UNII: 3OWL53L36A)	
silicon dioxide (UNII: ETJ7Z6XBU4)	
sodium lauryl sulfate (UNII: 368GB5141J)	
sodium stearyl fumarate (UNII: 7CV7WJK4UI)	
starch, corn (UNII: O8232NY3SJ)	
talc (UNII: 7SEV7J4R1U)	

Product Characteristics

Color	WHITE (white to off white)	**Score**	no score
Shape	ROUND (biconvex)	**Size**	12mm
Flavor		**Imprint Code**	RDY;329
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55111-329-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	09/09/2009	
2	NDC:55111-329-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	09/09/2009	
3	NDC:55111-329-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/09/2009	
4	NDC:55111-329-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	09/09/2009	
5	NDC:55111-329-78	10 in 1 CARTON	09/09/2009	
5	NDC:55111-329-79	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077461	09/09/2009	

Labeler - Dr. Reddy's Laboratories Limited (650562841)

Establishment

Name	Address	ID/FEI	Business Operations
Dr. Reddy's Laboratories Limited -		918608162	analysis(55111-328, 55111-329) , manufacture(55111-328,

FTO III		918608162	55111-329)