Nateglinide Tablets, USP
Rx only

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 ([trans-4-isopropylcyclohexane)carbonyl]-D-phenylalanine, is structurally unrelated to the oral sulfonylurea insulin secretagogues. The structural formula is as shown:

![Structural formula of Nateglinide](image)

Nateglinide is a white powder with a molecular weight of 317.43. It is freely soluble in methanol, ethanol, and chloroform; soluble in acetone and ether, and practically insoluble in water.

Nateglinide bisconex tablets contain 60 mg, or 120 mg, of nategline for oral administration.

Inactive Ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, 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
Nategline 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. Nategline interacts with the ATP-sensitive potassium (KATP) channel on pancreatic beta-cells. The subsequent opening of the beta-cell ATP-regulated K+ channels causes potassium efflux, membrane polarization, and insulin secretion.

Pharmacokinetics
Following oral administration immediately prior to a meal, nategline is rapidly absorbed with mean peak plasma drug concentrations (Cmax) generally occurring within 1 hour (Tmax) after dosing. When administered to patients with Type 2 diabetes over the dosage range 60 mg to 240 mg three times daily for one week, nategline demonstrated linear pharmacokinetics for both AUC and Cmax and was also found to be independent of dose in this patient population. Absolute oral bioavailability is expected to be approximately 73%. When given with or after a meal, the extent of nategline absorption (AUC) remains unaffected. However, there is a delay in the rate of absorption characterized by a decrease in Cmax and a delay in time to peak plasma concentration (Tmax). Plasma profiles are characterized by multiple concentration peaks when nategline is administered as a multiple dose.

Distribution
Based on data following intravenous (IV) administration of nategline, the steady-state volume of distribution of nategline is estimated to be approximately 1 liter in healthy subjects. Nategline is extensively bound (98%) to serum proteins, primarily serum albumin, and to a lesser extent to beta-globulin and alpha-globulin. Approximately 98% of the nategline is protein bound (98%) to serum proteins, primarily albumin. Patients with kidney disease have similar protein binding characteristics to nategline. Patients with severe renal impairment (CrCl ≤ 15 mL/min) have a reduced free fraction of nategline.

Excretion
Approximately 6% and 22% of nategline and its metabolites are rapidly and completely eliminated following oral administration. Within 6 hours after dosing, approximately 75% and 72% of the administered [14C]-nategline was recovered in the urine with 5% and 11% excreted as unchanged nategline in the urine. Eighty-three percent of the [14C]-nategline was excreted in the urine with 13% excreted in the feces. Approximately 16% of the [14C]-nategline was excreted in the urine as parent compound. In all studies of healthy volunteers and patients with Type 2 diabetes, nategline plasma concentrations declined with a half-life of approximately 1.5 hours. Consistent with this short elimination half-life, there was no apparent accumulation of nategline upon multiple dosing of up to 240 mg three times daily for 7 days.

Drug interactions
In vitro drug metabolism studies indicate that nategline is predominantly metabolized by the cytochrome P450 isozyme CYP3A4 (70%) and to a lesser extent CYP3A3 (30%). Nategline is a potential inhibitor of the CYP3A4 isozyme in vivo as indicated by its ability to inhibit the in vitro activity of isolated human liver microsomes. Nategline has a Ki of approximately 1 μM for CYP3A4 and 10 μM for CYP3A3.

In a randomized, multiple-dose crossover study, patients with Type 2 diabetes were administered 120 mg nategline 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.

Digoxin: When nategline 120 mg 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 digoxin.

Warfarin: When healthy subjects were administered nategline 120 mg three times daily 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 by nategline.

Diclofenac: Administration of morning and lunch doses of nategline 120 mg three times daily to healthy volunteers resulted in no significant changes to the pharmacokinetics of diclofenac.

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

Gender: No clinically significant differences in nategline pharmacokinetics were observed between men and women. Therefore, no dose adjustments are necessary for either gender.

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 nategline.

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 Cmax values as healthy matched subjects. Nategline exhibited reduced overall drug exposure. However, hemodialysis increased the apparent elimination half-life from 5.4 hours to 9.0 hours.

Hepatic Impairment: The peak and total exposure of nategline in non-hypoglycemic subjects was not statistically significantly greater than placebo.

Clinical Studies
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In a double-blind, placebo-controlled trial, patients with Type 2 diabetes who had been on a sulfonylurea for 3 months and who had a baseline HbA1c ≥ 7.0% were randomized to receive nategline (60 mg or 120 mg three times daily before meals) or glyburide 10 mg daily (three times daily before meals) for 12 weeks. Nategline was associated with significant reductions in mean HbA1c and mean FPG at endpoint compared to placebo randomized to glyburide.

Glyburide: Nategline Monotherapy Compared to Other Oral Antidiabetic Agents

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Nategline 60 mg three times daily before meals</th>
<th>Nategline 120 mg three times daily before meals</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>8.6</td>
<td>7.9</td>
<td>8.1</td>
</tr>
<tr>
<td>Difference from baseline (mean)</td>
<td>0.3</td>
<td>-0.1</td>
<td>-0.5</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>117</td>
<td>172</td>
<td>121</td>
</tr>
<tr>
<td>Difference from placebo (mean)</td>
<td>0.4</td>
<td>-0.5</td>
<td>-0.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>161</td>
<td>160</td>
<td>163</td>
</tr>
<tr>
<td>Change from baseline (mean)</td>
<td>0.4</td>
<td>-0.1</td>
<td>-0.1</td>
</tr>
<tr>
<td>Difference from placebo (mean)</td>
<td>1.6</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* p-value < 0.004

Nategline 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 HbA1c ≥ 7.0% were randomized to receive nategline (60 mg or 120 mg three times daily before meals) or glyburide 10 mg daily (three times daily before meals) for 12 weeks. Nategline was associated with significant increases in mean HbA1c and mean FPG at endpoint compared to placebo randomized to glyburide.

Metformin

In another randomized, double-blind, 24-week, active-placebo-controlled trial, patients with Type 2 diabetes who had been on a sulfonylurea for 3 months and who had a baseline HbA1c ≥ 7.0% were randomized to receive nategline (60 mg or 120 mg three times daily before meals), metformin 500 mg (three times daily), or combination of nategline 120 mg (three times daily before meals) and metformin 500 mg (three times daily). No patients experienced hypoglycemia that required third party assistance. Patients treated with nategline had statistically significant increases in weight compared to placebo (see Table 2).

Nategline Monotherapy Compared to Placebo

In a randomized, double-blind, placebo-controlled, 24-week study, patients with Type 2 diabetes (n=210) were randomized to receive either nategline (60 mg or 120 mg three times daily before meals) or placebo. Baseline HbA1c ranged from 6.3% to 8.4%. Fifty-seven percent of patients were previously untreated with oral antidiabetic therapy. Patients previously treated with antidiabetic medications were required to be on a stable dose for at least 2 months prior to randomization. The reductions in mean HbA1c and mean FPG at endpoint compared to placebo were significantly greater than the reductions in these variables associated with placebo (see Table 2). Relative to placebo, nategline 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 HbA1c and mean FPG for nategline monotherapy were similar to those for metformin monotherapy (see Table 2). Among the subset of patients previously treated with other antidiabetic agents, primarily glyburide, HbA1c in the nategline monotherapy group increased slightly from baseline, whereas HbA1c was reduced in the metformin monotherapy group (see Table 2).

Nategline Combination Therapy

In the active and placebo-controlled study of metformin and nategline plus metformin, patients with Type 2 diabetes who had previously received sulfonylurea monotherapy were randomized to either nategline or metformin monotherapy (see Table 2). No patients experienced an episode of hypoglycemia that required third party assistance. Compared to placebo, nategline monotherapy was associated with a statistically significant increase in weight, while no significant change in weight was observed with combined nategline and metformin (see Table 2).
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.

4. Moderate-to-severe hepatic dysfunction has not been studied.

5. Nursing Mothers

Nateglinide is not genotoxic in the in vitro Ames test, the micronucleus test, or the chromosomal aberration test 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 800 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: In rats at doses up to 1000 mg/kg oral nateglinide produced no increased fetal resorption or increased fetal and neonatal death. In rabbits, nateglinide dose of 120 mg, three times daily before meals. In the rabbit, diabetic ketone development was adversely affected and the incidence of gallbladder agenesis or small gallbladder was increased at a dose of 1000 mg/kg oral nateglinide three times the human therapeutic exposure with a recommended nateglinide dose of 120 mg, three times daily before meals.

In rabbits, nateglinide in combination with metformin resulted in decreased fetal weight in a manner similar to that seen for metformin alone. However, the clinical significance of these findings is unknown.

Maternal Toxicity: Administration of nateglinide to pregnant rabbits did not produce any evidence of embryotoxicity or fetal toxicity. The dose at which nateglinide may be used in pregnant women is not known.

Nursing Mothers: Nateglinide therapy should be used with caution in patients with moderate-to-severe liver disease (see PRECAUTIONS, Hepatic Impairment). 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 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 HbA1c when treatment is initiated.

Dosing in Geriatric Patients

Clinical trials have not been conducted in patients over 75 years of age. However, the safety and efficacy of nateglinide in this age group is expected to be similar to that in younger adults. The recommended starting dose is 60 mg three times daily before meals. No dosage adjustment is necessary in patients with mild-to-moderate renal insufficiency or in patients with mild hepatic insufficiency. Dosing in Obese Patients: There are no adequate and well-controlled studies in obese patients with moderate-to-severe hepatic dysfunction has not been studied.

Dosage in Moderate-to-Severe Liver Disease

In patients with moderate-to-severe liver disease (see PRECAUTIONS, Hepatic Impairment), nateglinide therapy should be used with caution.

DOSAGES AND ADMINISTRATION

Nateglinide Tablets, USP are supplied as tablets containing 60 mg nateglinide or 120 mg nateglinide. The tablets are light yellow, round, biconvex, beveled edge tablets debossed with ‘N 984’ on one side and plain on the other side.

120 mg Tablets

Orange color coated, oval shaped biconvex, tablet debossed with ‘P 985’ on one side and plain on the other side.

Dosage and Administration

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