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Nateglinide

Christopher J. Dunn and *Diana Faulds*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Nateglinide is a novel D-phenylalanine derivative that inhibits ATP-sensitive K^+ channels in pancreatic β-cells in the presence of glucose and thereby stimulates the prandial release of insulin.

▲ Nateglinide reduces fasting and mealtime blood glucose levels in animals, healthy volunteers, and patients with type 2 (non–insulin-dependent) diabetes mellitus, and produces prompt prandial insulin responses with return to baseline insulin levels between meals.

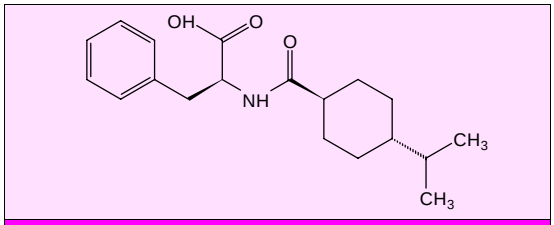
▲ In randomised, double-blind 24-week studies in patients with type 2 diabetes, oral nateglinide 120mg 3 times daily before meals improved glycaemic control significantly relative to placebo.

▲ Nateglinide 120mg plus metformin 500mg, both 3 times daily, conferred greater glycaemic improvement than either drug given alone, and nateglinide 60 or 120mg 3 times daily plus metformin 1g twice daily was superior to metformin plus placebo.

▲ Nateglinide 120mg 3 times daily significantly reduced hyperglycaemia relative to placebo in a 16-week double-blind study in patients with type 2 diabetes mellitus. Combination therapy with troglitazone 600mg daily produced significantly better glycaemic control than either drug given as monotherapy.

▲ Mild hypoglycaemia was the most frequently reported adverse event (1.3% of patients) after treatment with nateglinide 120mg 3 times daily in a 16-week clinical study. No clinically significant abnormalities in laboratory results, ECGs, vital signs or physical examination findings have been noted in patients taking the drug.

Features and properties of nateglinide (A 4166, AY 4166, SDZ DJN 608, YM 026, senaglinide)	
Indications	
Management of type 2 (non–insulin-dependent) diabetes mellitus	
Mechanism of action	
Enhances first phase insulin secretion	Inhibition of ATP-sensitive K^+ channels
Dosage and administration	
Most common dosage in clinical trials	120mg 3 times daily before meals
Route of administration	Oral
Pharmacokinetic profile	
Peak plasma concentration	7.2 mg/L after 3 oral doses of 120mg
Time to peak plasma concentration	0.5–1.9h after 7 days' treatment with 60 to 240mg 3 times daily
Renal clearance	1.2 L/h
Elimination half-life	≈1.5h
Metabolism	Via mixed function oxidases
Route of elimination	≈80% in urine
Adverse events	
Most frequent	Symptoms indicative of mild hypoglycaemia



Nateglinide

Type 2 (non–insulin-dependent) diabetes mellitus is characterised by impaired pancreatic insulin secretion and/or peripheral insulin resistance. After meals, patients with type 2 diabetes mellitus typically exhibit an impaired first phase insulin response and delayed second phase secretion, with inadequate release of insulin overall in relation to plasma glucose levels.[1]

Sulphonylureas have been used for many years to promote insulin secretion and to reduce overall blood glucose levels throughout the day in patients with type 2 diabetes mellitus, but can cause severe hypoglycaemia, especially when meals are missed.[1] Nateglinide, a derivative of D-phenylalanine, belongs to a novel group of rapidly acting insulinotropic agents designed to stimulate insulin secretion when needed (i.e. at mealtimes) with return to basal insulin levels between meals. These agents have been developed to reduce the risk of hypoglycaemia associated with pharmacological management and to decrease the likelihood of secondary treatment failure related to pancreatic β-cell exhaustion.[1,2]

1. Pharmacodynamic Profile

Cellular Mechanism of Action

• Nateglinide mediates the release of insulin from pancreatic β-cells by binding competitively to cell membrane sulphonylurea receptors, which leads to closure of ATP-sensitive K^+ (K_{ATP}) channels [the K_{ATP} channel appears to be a regulatory protein containing the sulphonylurea receptor and an inwardly rectifying K^+ channel (Kir6.2) that serves as a pore-forming subunit[3]]. This results in cell depolarisation and activation of voltage-dependent L-type Ca^{2+} channels, which promotes entry of Ca^{2+} ions into cells and subsequent exocytosis of insulin-containing secretory granules.[4-6]

• The competitive interaction of nateglinide with the human sulphonylurea receptor 1 (SUR1) has been demonstrated in *in vitro* receptor binding studies in RIN-m5F (a rat islet cell tumour β-cell line) membranes and HEK-293 (human embryonic kidney) cells expressing recombinant SUR1 receptors.[4] Receptor binding and K_{ATP} channel activity results were consistent with more rapid onset and shorter duration of action of nateglinide than the carbamoylmethylbenzoic acid derivative repaglinide and the sulphonylureas.

• The order of potency in terms of displacement of [^{3}H]-glibenclamide in RIN-m5F membranes was glibenclamide > glimepiride > repaglinide > glipizide > nateglinide > L-nateglinide > tolbutamide.[4] The estimated dissociation half-life of nateglinide from the RIN-m5F SUR1 receptor was approximately 1 second; values of 2.9 and 63 minutes (biphasic dissociation kinetics) were reported for glibenclamide. The corresponding value for repaglinide was approximately 2 minutes.

• Binding of nateglinide and tolbutamide but not repaglinide to an additional intracellular site has been indicated by increases in Ca^{2+}-induced exocytosis in isolated rat pancreatic α- and β-cells.[7] A binding site specific for nateglinide has also been suggested by receptor binding studies in cells from the hamster pancreatic β-cell line HIT T-15.[8]

• In the presence of glucose 2.8 mmol/L, addition of nateglinide 3 to 30 μmol/L resulted in rapid and concentration-dependent increases in intracellular Ca^{2+} concentrations in isolated rat pancreatic β-cells.[2] The cellular response to nateglinide was completely and reversibly blocked by nitrendipine (an L-type Ca^{2+} channel antagonist) and diazoxide (which opens K_{ATP} channels).[2]

• In contrast to glibenclamide and repaglinide, inhibition by nateglinide of K_{ATP} current is enhanced *in vitro* in the presence of high concentrations of glucose. Patch clamp studies in rat pancreatic β-cells showed concentration-dependent inhibition

of diazoxide-induced K_{ATP} current activation in the presence of glucose 5 mmol/L; drug concentrations required for 50% current inhibition (IC_{50}) were 7.4 μmol/L for nateglinide, 16.6 nmol/L for glibenclamide and 5.0 nmol/L for repaglinide.[9] In the presence of glucose 16 mmol/L, the IC_{50} for nateglinide was reduced to 2.5 μmol/L ($p = 0.05$), whereas IC_{50} values for glibenclamide and repaglinide were slightly increased (to 18.9 and 7.4 nmol/L, respectively).

- Patch clamp data from rat islet cells showed reversible inhibition of whole cell K_{ATP} currents with no change in single channel conductance by nateglinide at concentrations above 0.1 μmol/L.[10] Nateglinide 0.23 μmol/L and tolbutamide 12.8 μmol/L produced half-maximal inhibition of the whole cell K_{ATP} current. In other studies, IC_{50} values of 0.2 and 0.008 μmol/L were reported for nateglinide and repaglinide, respectively,[7] and the order of potency of inhibition of K_{ATP} channels in rat pancreatic β-cells was repaglinide > glibenclamide > nateglinide.[4] Nateglinide had no effect on L- or T-type Ca^{2+} channel or time-dependent outward currents.[10]

- Kinetic studies in rat pancreatic β-cells showed that the onset of inhibition of K_{ATP} current by nateglinide [time to 50% inhibition of channel activity ($t_{½on}$) = 4.1 minutes] was similar to that of glibenclamide ($t_{½on}$ = 4.2 minutes) but more rapid than that of repaglinide ($t_{½on}$ = 12 minutes).[4] Times to return to 50% inhibition of channel activity from maximal inhibition after withdrawal of test drugs ($t_{½off}$) were 35, 69 and 175 minutes, respectively.

- Patch clamp analysis of isolated rat β-cells and rat cardiac myocytes, and smooth muscle cells from porcine coronary arteries and rat aorta, showed selectivity of nateglinide and repaglinide, but not glibenclamide, for pancreatic β-cells.[3] All 3 drugs caused 62 or 63% inhibition of K_{ATP} channels at equipotent concentrations ($2 \times IC_{50}$) in β-cells, but only nateglinide and repaglinide were associated with statistically significantly ($p < 0.05$) lower inhibition of similar channels in porcine coronary arterial and rat aortic tissue.[3]

Effects on Blood Glucose and Insulin Levels

Animal Studies

- Insulin secretion from freshly isolated rat pancreatic islet cells was stimulated by nateglinide at concentrations ranging from 3 to 300 μmol/L in the presence of glucose 2.8 mmol/L.[11] The maximal insulinotropic effect of nateglinide was similar to that of glibenclamide 0.03 μmol/L, gliclazide 1 μmol/L or tolbutamide 30 μmol/L. Plasma insulin levels increased significantly within 30 minutes of oral administration of nateglinide 5 mg/kg in fasting beagles and returned to baseline levels within 2 hours.[11]

- In fasting beagles, oral nateglinide 5 mg/kg caused maximal hypoglycaemia 1 hour after administration, with normalisation of blood glucose levels after 6 hours (hypoglycaemia was maintained beyond this period with gliclazide 1 mg/kg, tolbutamide 10 mg/kg or glibenclamide 0.1 mg/kg).[11] Normalisation of blood glucose levels was seen after 3 hours in fasting rats who received nateglinide 25, 50 or 100 mg/kg.[12]

- Addition of nateglinide 3 μmol/L did not affect basal insulin secretion in an isolated rat pancreas perfused with glucose 5 mmol/L.[13] However, the first and second phases of insulin secretion were stimulated and the curve of insulin response to glucose was shifted to the left when the same concentration of nateglinide was used in the presence of glucose 7.5 to 15 mmol/L.[13]

- Both nateglinide 1 μmol/L and repaglinide 0.01 μmol/L stimulated insulin and somatostatin release but not glucagon output from isolated rat pancreas perfused with glucose 5.6 mmol/L.[14] The insulin response to nateglinide was rapid, with a marked first secretory peak after 46 minutes of perfusion. A less marked initial secretory peak was seen after 51 minutes with repaglinide.

- Insulin output declined rapidly (within 10 minutes) to baseline levels after withdrawal of nateglinide, whereas a slow decline was seen after cessation of exposure to repaglinide.[14] The more rapid reversal of effect of nateglinide was demonstrated by calculation of paired ratios of mean

hormonal outputs (after : during drug exposure) of 21.8% for nateglinide and 83% for repaglinide ($p < 0.02$).

- In a similar study,[15] nateglinide 3 and 30 μmol/L stimulated insulin secretion but had little effect on glucagon output in the presence of glucose concentrations of 8 and 11 mmol/L.

Studies in Humans

- Mean first phase insulin secretion was 1.87 or 0.01 mU/mmol glucose ($p < 0.01$ between groups), respectively, when nateglinide 60mg or placebo was given 20 minutes before an intravenous glucose challenge (0.3 g/kg) in a double-blind study in 10 patients with type 2 diabetes mellitus.[16]

- Fourteen healthy volunteers received single oral doses of placebo, nateglinide 120mg, or repaglinide 0.5 or 2mg 10 minutes before a standardised 800 kcal breakfast in a randomised, nonblind crossover study.[17] The area under the curve (AUC) of plasma glucose level versus time showed reduction of mealtime blood glucose excursions for up to 2 hours after administration of nateglinide, with a return to predose levels after 4 hours.

- A more prolonged hypoglycaemic effect (up to 6 hours after administration) was noted with repaglinide 2mg, with a return to baseline (predose) plasma glucose levels not being seen for approximately 8 hours.[17] Peak prandial plasma insulin levels were seen at 0.78 and 0.92 hours with nateglinide 120mg and repaglinide 2mg, respectively. Plasma insulin levels with nateglinide were similar to those seen with placebo from 1.5 hours after administration, whereas plasma insulin levels remained elevated for up to 4 hours with repaglinide.[17]

- Administration of nateglinide 10 minutes before meals produced rapid and short-lived stimulation of insulin release and blunted mealtime glucose excursions in a randomised, double-blind, crossover study in 10 patients with type 2 diabetes mellitus.[18] Nateglinide 30, 60 or 120mg or placebo was given 3 times daily for 7 days, with plasma insulin and glucose levels being monitored on day 7. Compared with placebo, mean blood glucose AUC values were reduced over a 4-hour postprandial period by 48 and 50%, respectively, after administration of nateglinide 60 and 120mg ($p < 0.05$ *vs* placebo and nateglinide 30mg).[18]

- After 8 weeks' double-blind treatment in 152 patients, reductions relative to baseline in incremental AUC of plasma glucose level versus time after a liquid meal challenge were 4.94 and 2.71 mmol/L · h with nateglinide 120mg 3 times daily before meals and glibenclamide 10mg daily, respectively ($p < 0.05$ between treatments).[19] Both treatments reduced overall plasma glucose levels to a similar extent, but whereas nateglinide primarily reduced mealtime glucose excursions, glibenclamide acted primarily on fasting plasma glucose (FPG) levels (reductions relative to baseline of 2.9 and 1.0 mmol/L with glibenclamide and nateglinide, respectively; $p < 0.05$).

- The effect of nateglinide on mealtime plasma glucose excursions has also been shown in a 24-week randomised double-blind study in 685 patients with type 2 diabetes mellitus.[20] Reductions relative to baseline in adjusted AUC of plasma glucose level versus time after a liquid meal challenge were 0.6, 2.1, 1.1 and 2.5 mmol/L · h for placebo, nateglinide (120mg 3 times daily before meals), metformin (500mg 3 times daily with meals) and nateglinide plus metformin, respectively. The AUC reductions for nateglinide monotherapy and combination therapy were statistically significantly greater than those for placebo and metformin monotherapy.

- Plasma glucose levels after meals were reduced to a significantly greater extent with nateglinide 120mg plus metformin 500mg (both 3 times daily 10 minutes before meals for 1 day) than with either drug alone in a randomised, double-blind, 2-way crossover study in 12 patients with type 2 diabetes mellitus. The overall mean reduction in plasma glucose level over 15 hours (1 day's treatment) was 1.4 mmol/L with nateglinide plus metformin, whereas reductions of 1.1 and 0.9 mmol/L were reported with metformin plus placebo and nateglinide alone, respectively (both $p < 0.001$ *vs* nateglinide plus metformin).[21] The AUC of plasma

glucose level versus time over 15 hours was significantly ($p < 0.001$) smaller with nateglinide plus metformin than with either monotherapy.

2. Pharmacokinetic Profile

- The mean peak plasma concentration (C_{max}) of nateglinide was 7.2 mg/L after the third 120mg dose in a study in which 11 evaluable patients with type 2 diabetes received 3 doses of the drug (each 5 minutes before a meal) over 1 day.[21] The mean time to attain C_{max} (t_{max}) was 0.82 hours. t_{max} of nateglinide ranged from 0.5 to 1.9 hours in another study in which patients with type 2 diabetes mellitus received nateglinide 60, 120, 180 or 240mg 3 times daily for 7 days.[22]

- Relative to reference data from fasting volunteers, administration of a nateglinide 60mg tablet 10 minutes before a high fat breakfast resulted in a 12% increase in mean C_{max} and 52% decrease in mean t_{max}. There was no significant effect of food on the extent of absorption of the drug (as shown by AUCs of plasma drug concentrations versus time). When nateglinide was given after the meal, the rate of absorption was decreased (34% decrease in mean C_{max} and 22% increase in mean t_{max}).[23]

- Under fasting conditions in the above study, nateglinide was eliminated rapidly [mean elimination half-life ($t_{½\beta}$) 1.4 hours].[23] In another study, mean $t_{½\beta}$ was 1.8 hours after the third of three 120mg doses (each given 5 minutes before a meal) in 8 patients with type 2 diabetes mellitus.[21]

- The mean apparent total clearance of nateglinide after a single 120mg dose was 8.4 L/h in 8 healthy individuals and 7.7 L/h in 8 patients with hepatic cirrhosis in a nonblind parallel group pharmacokinetic study.[24] Other data show a mean renal clearance of 1.2 L/h for nateglinide,[23] attributable mainly to active tubular secretion, although only 13 to 14% of the administered dose was recovered unchanged in the urine in these patients. Overall, nateglinide is present predominantly as the parent compound in blood. There is no evidence of accumulation or any change in bioavailability over time with long term administration of nateglinide.[25]

- Nateglinide is extensively metabolised by the mixed function oxidase system; the main metabolites found in humans result from hydroxylation of the isopropyl side chain, with minor metabolites being formed by diol, isoprene or glucuronide conjugate formation. Results of *in vitro* experiments in human hepatic microsomes suggest the involvement of cytochrome P450 (CYP) isoenzymes CYP3A4 and CYP2C9.[23,26] Nateglinide is reported to be eliminated predominantly [approximately 80% of the total dose (i.e. parent drug plus metabolites)] via the urine.[24]

- Mild to moderate hepatic cirrhosis had no significant effect on the pharmacokinetics of a single oral dose of nateglinide 120mg in 8 individuals with hepatic dysfunction who were compared with 8 demographically matched healthy individuals. The mean total body clearance was decreased by 8.4% and the mean renal clearance increased by 12.4% in patients with cirrhosis relative to healthy volunteers. Nateglinide was 97% bound to plasma proteins in both healthy individuals and those with cirrhosis. Mean Cmax of nateglinide was 7.7 mg/L in patients with cirrhosis and 5.6 mg/L in healthy volunteers.[24]

- Administration of metformin with nateglinide did not affect the pharmacokinetics of either drug in a study in patients with type 2 diabetes mellitus.[21] A study in healthy volunteers has shown no evidence of any effect on the pharmacokinetics of digoxin or nateglinide when both drugs are used together.[27]

3. Therapeutic Trials

Clinical trials with nateglinide (as monotherapy or in combination with other oral antihyperglycaemic agents) have been carried out in a range of patients with type 2 diabetes mellitus. In phase III clinical trials, patients with inadequate glycaemic control [defined as blood levels of glycated haemoglobin (HbA_{1c}) of 6.8 to 11%] by diet and exercise[20,28] or maximal dosages of metformin[29] were recruited. Blood levels of HbA_{1c}, which give an indication of overall glycaemic control over a period of several weeks, and FPG levels, were used

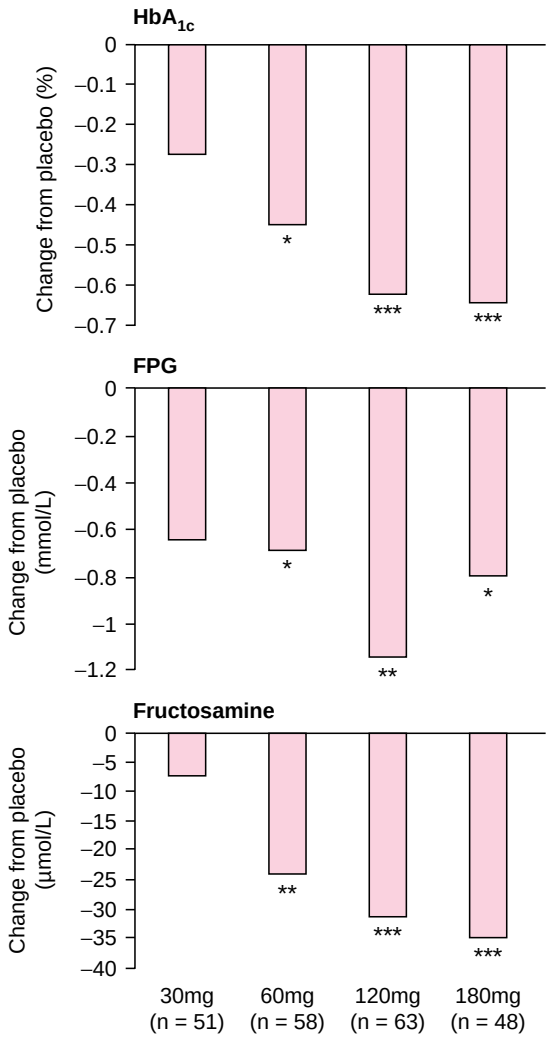


Fig. 1. Improvements in clinical end-points after treatment with nateglinide for 12 weeks. 289 patients with type 2 diabetes mellitus were randomised to oral therapy with 1 of 4 dosages of nateglinide or placebo, with each dose taken 10 minutes before meals. End-points were measured before (baseline) and at the end of 12 weeks' treatment. Mean changes after 12 weeks with each dosage of active treatment were compared with those in patients receiving placebo.[30] **FPG** = fasting plasma glucose levels; **HbA_{1c}** = haemoglobin A_{1c} levels in blood; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs* placebo.

as key clinical end-points across the clinical study programme. Overall, the studies showed nateglinide to improve glycaemic control significantly, with the greatest reductions in HbA_{1c} and FPG levels being obtained when the drug is used in combination with other agents.

Phase II Study

- Nateglinide improved glycaemic control in a dose-dependent manner in a double-blind placebo-controlled study in which 289 patients with type 2 diabetes mellitus were randomised.[30] Medication (nateglinide 30, 60, 120 or 180mg or placebo 3 times daily) was taken 10 minutes before meals each day for 12 weeks. As shown in figure 1, statistically significant improvements relative to placebo in blood levels of HbA_{1c} and fructosamine (glycated albumin, indicative of overall glycaemic control over approximately 2 weeks) and in FPG levels were noted after 12 weeks' treatment in patients receiving nateglinide 60 to 180mg 3 times daily.

- Statistically significant improvements relative to placebo in HbA_{1c} and fructosamine levels in blood were also seen with nateglinide 60 and 180mg 3 times daily; the 30mg dosage had no statistically significant effect on any of the measured parameters of glycaemic control (fig. 1).[30] There were no statistically significant changes relative to placebo after nateglinide treatment in fasting levels of triglyceride or in low and high density lipoprotein and total cholesterol levels in serum.

Phase III Studies

- In a randomised study in 685 patients with type 2 diabetes mellitus inadequately controlled by diet and exercise, mean HbA_{1c} and FPG levels were statistically significantly reduced relative to placebo after 24 weeks' double-blind treatment with nateglinide 120mg 3 times daily before meals, metformin 500mg 3 times daily with meals or a combination of these 2 drugs (fig. 2).[20] In the placebo group, the mean HbA_{1c} level increased by 0.5% and mean FPG level by 0.4 mmol/L from baseline over the 24-week study period.

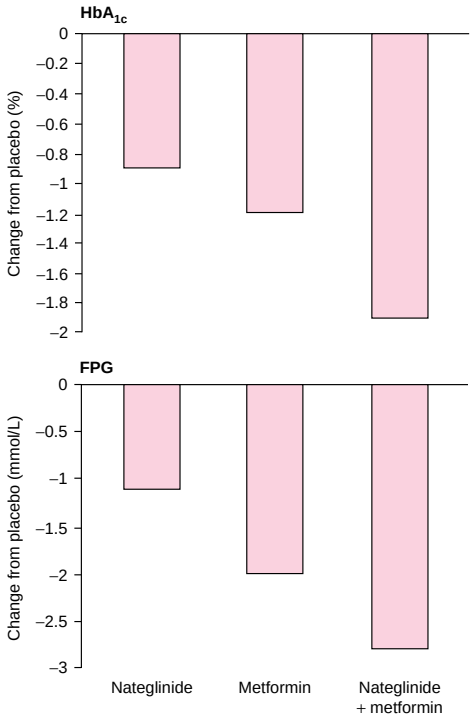


Fig. 2. Effect of nateglinide and/or metformin treatment on glycaemic control. Patients with type 2 diabetes mellitus poorly controlled by diet and exercise were randomised to double-blind treatment with placebo (n = 167), nateglinide 120mg 3 times daily before meals (n = 175), metformin 500mg 3 times daily with meals (n = 175) or a combination of the 2 drugs (n = 168) for 24 weeks.[20] Mean changes relative to placebo are shown for glycated haemoglobin (HbA_{1c}) and fasting plasma glucose (FPG) levels. For both clinical end-points, results in all treatment arms were statistically significantly different from each other, with the largest reductions being seen with combination treatment (p values not provided).

• Mean bodyweight decreased by 0.4kg from baseline across the 24-week study period in the placebo group. There was no change in bodyweight in the metformin group, and small increases only in the nateglinide (0.9kg) and combination treatment (0.2kg) groups.[20]

• Nateglinide in combination with metformin was compared with metformin monotherapy in a 24-week randomised, double-blind placebo-controlled study in 467 patients with inadequate glycaemic control with dietary modification and maximal dosages of metformin (≥1.5g daily).[29] Patients had a mean age of 57 years, mean BMI 29 kg/m^2 and mean HbA_{1c} level 8.1%, and were randomised to receive nateglinide 60 or 120mg or placebo 3 times daily before meals in addition to metformin 1g twice daily.

• After 24 weeks of study therapy, mean reductions (expressed as a percentage of total haemoglobin) from baseline in HbA_{1c} levels were 0.4 and 0.6%, respectively ($p < 0.01$ *vs* metformin plus placebo), in patients receiving nateglinide 60 or 120mg in addition to metformin.[29] Both dosages of nateglinide also had a statistically significant beneficial effect on FPG levels after 24 weeks (fig. 3).

• A further double-blind study in which patients were randomised to treatment with placebo (n = 148), nateglinide 120mg 3 times daily before meals (n = 150), troglitazone 600mg daily (n = 151) or combination treatment with nateglinide and troglitazone (n = 150) showed glycaemic improvement with all active treatments over 16 weeks.[28] HbA_{1c} and FPG levels were reduced relative to placebo with combination therapy (by 2.2% and 3.9 mmol/L, respectively) and with nateglinide (by 1% and 1.2 mmol/L) and troglitazone (by 1.2% and 2.7 mmol/L) alone ($p < 0.001$ *vs* placebo for all results). Over the 16 weeks of the study, mean HbA_{1c} and FPG levels rose by 0.5% and 0.7 mmol/L from baseline, respectively, in the placebo group.

• Combination therapy was statistically significantly better ($p < 0.001$) in terms of HbA_{1c} and FPG levels than either monotherapy in this trial.[28] Troglitazone monotherapy was associated with a significantly greater reduction than nateglinide monotherapy in FPG levels ($p < 0.001$).

4. Tolerability

• Oral nateglinide (30, 60, 120 and 180mg 3 times daily) was well tolerated in a randomised, double-blind, placebo-controlled 12-week phase II trial in 289 evaluable patients with type 2 diabetes mellitus.[30] Rates of discontinuation of treatment for

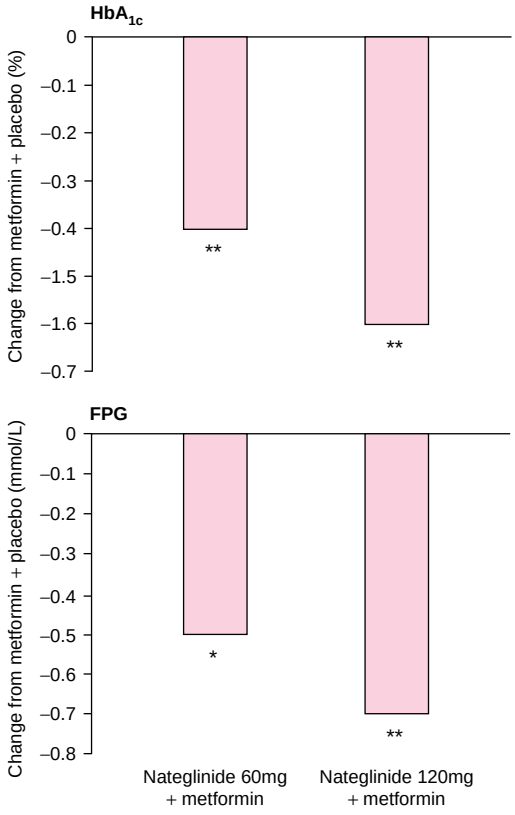


Fig. 3. Effects of nateglinide in combination with metformin. A population of 467 patients with type 2 diabetes mellitus inadequately controlled by diet and metformin therapy received metformin 1g twice daily plus nateglinide 60 or 120mg or placebo 3 times daily (before meals) for 24 weeks in a randomised double-blind trial. Mean parameters were recorded before (baseline) and after 24 weeks' treatment.[29] **FPG** = fasting plasma glucose levels; **HbA_{1c}** = haemoglobin A_{1c} levels in blood; * $p < 0.05$, ** $p < 0.01$ *vs* placebo plus metformin.

adverse events were 3.3% in the placebo group and 2.2% across all patients receiving nateglinide. The overall incidence of adverse events was higher in the pooled nateglinide group (n = 229) than in the placebo group (n = 60) [49.3 *vs* 35%]; events were not dosage-related.

- The most common adverse events in the pooled nateglinide group were suggestive of hypoglycaemia, and included increased sweating (7%), tremor (6.1%), dizziness (3.1%), increased appetite (2.6%) or asthenia (1.7%).[30] Of patients in the nateglinide 120mg group who showed symptoms, only 3 had plasma glucose levels of 3.3 mmol/L or less. No patients withdrew from the study because of this adverse event, and most episodes were linked to strenuous exercise or a missed or delayed meal.

- Confirmed hypoglycaemia (plasma glucose level ≤3.3 mmol/L) was reported in 0.7% of patients receiving metformin 1g twice daily plus placebo, no patients receiving metformin plus nateglinide 60mg 3 times daily and 3.1% of those receiving metformin plus nateglinide 120mg 3 times daily in a randomised, double-blind 24-week study in 467 evaluable individuals.[29] Overall, more patients who received metformin with nateglinide than with placebo showed symptoms indicative of hypoglycaemia, but all events were mild and resolved rapidly with treatment. No clinically significant laboratory or electrocardiographic changes were noted.

- Mild hypoglycaemia was reported in 1.3% of 150 patients who received nateglinide 120mg 3 times daily, 1.3% of 151 who received troglitazone 600mg daily, 7.3% of 150 who received combination therapy with both drugs and 2% of 148 placebo recipients in a 16-week randomised double-blind study.[28] No patients who received nateglinide alone showed clinically significant changes (defined as 3 times upper limit of normal range) in serum levels of ALT or AST.

5. Nateglinide: Current Status

Nateglinide is a novel first phase insulin secretion enhancer that has been launched in Japan and is in late phase clinical trials in other countries for the management of type 2 diabetes mellitus.

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Correspondence: *Christopher J. Dunn*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz