

# Hypoglycemics, Meglitinides Review

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## Hypoglycemics, Meglitinides Review

### FDA-Approved Indications

Drug	Manufacturer	Indications
nateglinide (Starlix <sup>®</sup> ) <sup>1</sup>	generic	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
repaglinide (Prandin <sup>®</sup> ) <sup>2</sup>	Novo Nordisk	Adjunct to diet and exercise in patients with type 2 diabetes who cannot be controlled by diet and exercise alone.  In combination with metformin, rosiglitazone or pioglitazone in patients who cannot be controlled by diet and exercise plus monotherapy with any of the following: metformin, sulfonylureas, rosiglitazone, or pioglitazone.
repaglinide/ metformin (PrandiMet <sup>™</sup> ) <sup>3</sup>	Novo Nordisk	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a meglitinide and metformin or who have inadequate glycemic control on a meglitinide alone or metformin alone.

### Overview

Diabetes was the seventh leading cause of death listed on U.S. death certificates in 2006.<sup>4</sup> It is estimated that 23.6 million people in the United States have diabetes. In adults, type 2 diabetes accounts for about 90 to 95 percent of all diagnosed cases of diabetes. Improved glycemic control benefits patients with either type 1 or type 2 diabetes. In general, for every one percent reduction in HbA<sub>1c</sub>, the risk of developing microvascular diabetic complications (eye, kidney, and nerve disease) is reduced by 40 percent.<sup>5</sup>

In addition to exogenous insulin, there are several pathways by which blood glucose is regulated in diabetic patients. The meglitinides, nateglinide (Starlix) and repaglinide (Prandin), increase insulin secretion to help control post-prandial blood glucose elevations.

The 2009 update to the American Diabetes Association (ADA) consensus algorithm for the medical management of hyperglycemia in type 2 diabetes does not list the meglitinides in its two tier treatment algorithm.<sup>6</sup> However, the meglitinides may be beneficial in select patients. The ADA consensus statement does note that repaglinide is more effective in lowering HbA<sub>1c</sub> than nateglinide and nearly as effective as metformin or the sulfonylureas.

### Pharmacology<sup>7,8,9</sup>

The meglitinides are non-sulfonylurea hypoglycemic agents used in the management of type 2 diabetes mellitus. These agents lower blood glucose levels by stimulating the release of insulin from the pancreas. Therefore, they are dependent on functioning beta cells in the pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations.

The meglitinides bind to a non-sulfonylurea binding site on the pancreatic beta cell membrane. This leads to the closing of ATP-dependent potassium channels in the beta cell membrane and the opening of calcium channels. The resulting increased calcium influx induces insulin secretion. The ion channel mechanism is highly tissue-selective with low affinity for heart and skeletal muscle.

Metformin is a biguanide-type antihyperglycemic agent. It increases peripheral uptake and utilization of glucose, resulting in a reduction in hepatic gluconeogenesis, a reduction in glucose absorption from the gastrointestinal tract, and an improvement in insulin sensitivity of peripheral tissue.

### Pharmacokinetics

Drug	Bioavailability (%)	T <sub>max</sub> (hr)	Half-life (hr)	Metabolism	Excretion (%)
metformin (Glucophage) <sup>10</sup>	50-60	--	6.2-17.6	None	urine: > 90
nateglinide (Starlix) <sup>11,12</sup>	73	≤1	1.5	Hepatic (2C9 and 3A4); less potent metabolites	urine: 83 feces: 10
repaglinide (Prandin) <sup>13</sup>	56	≤1	1	Hepatic (2C8 and 3A4); three metabolites which do not contribute to glucose lowering effect	urine: 8 feces: 90

Combination repaglinide/metformin (PrandiMet) tablets have been found to be bioequivalent to the individual drugs administered together.

### Contraindications/Warnings<sup>14,15,16,17</sup>

Nateglinide (Starlix) and repaglinide (Prandin) are both contraindicated in type 1 diabetics, patients with diabetic ketoacidosis, and patients with a known hypersensitivity to the drug or its inactive ingredient. Repaglinide is contraindicated in patients also taking gemfibrozil, and repaglinide/metformin (PrandiMet) is contraindicated in patients receiving both gemfibrozil and itraconazole.

Any product containing metformin is contraindicated in patients with any of the following: renal disease or renal dysfunction (serum creatinine  $\geq 1.5$  mg/dL for males and  $\geq 1.4$  mg/dL for females), acute or chronic metabolic acidosis, including diabetic ketoacidosis, acute myocardial infarction, septicemia, pregnancy, or known hypersensitivity to metformin or other ingredients in the drug formulation. Due to the metformin component, the labeling for combination repaglinide/metformin (PrandiMet) contains a black box warning related to an increased risk of lactic acidosis, especially in patients with renal impairment, sepsis, dehydration, excessive alcohol intake, hepatic impairment, or acute congestive heart failure. If lactic acidosis is suspected, combination repaglinide/metformin should be discontinued and the patient should be hospitalized immediately. Because metformin can cause vitamin B12 deficiency, patients being treated with any product containing metformin should have hematological parameters assessed annually.

Combination repaglinide/metformin should be temporarily discontinued in patients receiving iodinated contrast for radiological studies. Patients should also be warned against excessive alcohol intake while taking combination repaglinide/metformin due to the effect of alcohol on lactate metabolism.

Repaglinide should not be used with NPH insulin. During times of stress, nateglinide and repaglinide therapy may need to be discontinued and insulin started.

**Drug Interactions**<sup>18,19,20</sup>

Close monitoring of blood glucose is recommended when adding or discontinuing drugs that can induce hyperglycemia. When highly protein-bound drugs such as NSAIDs, salicylates, sulfonamides, coumarins, and beta-blockers are initiated or discontinued during therapy, monitor for hypoglycemia or loss of glycemic control. Other drugs such as thiazides, corticosteroids, thyroid products, estrogens, calcium channel blockers, and sympathomimetic agents may reduce the hypoglycemic effects of the meglitinides. When starting or stopping therapy with one of these agents, monitor for changes in glycemic control.

Gemfibrozil, itraconazole, and their combination have been shown to elevate repaglinide (Prandin) levels in healthy volunteers. Postmarketing events of serious hypoglycemia have been reported in patients taking both repaglinide and gemfibrozil. Repaglinide exposures are increased more than 20-fold in patients taking both gemfibrozil and itraconazole, therefore concurrent use of these agents is contraindicated. Ketoconazole, simvastatin, clarithromycin, levonorgestrel, and ethinyl estradiol have also been demonstrated to elevate repaglinide levels in healthy volunteers. Because repaglinide is partially metabolized by CYP2C8 and CYP3A4, any product containing repaglinide should be used with caution in patients taking inhibitors and/or inducers of these enzyme systems.

Although nateglinide (Starlix) is metabolized by the CYP450 system, nateglinide has no clinically significant drug interactions due to this mechanism noted at this time.

Cationic drugs (e.g., digoxin, ranitidine, triamterene) eliminated by renal tubular secretion may interfere with metformin elimination. As such, combination repaglinide/metformin (PrandiMet) should be used cautiously with these agents.

**Adverse Effects**

Drug	URI	Diarrhea	Back pain	Hypoglycemia	Dizziness	Headache
nateglinide (Starlix) <sup>21</sup> n=1,441	10.5 (8.1)	3.2 (3.1)	4.0 (3.7)	2.4 (0.4)	3.6 (2.2)	nr
repaglinide (Prandin) <sup>22</sup> n=352	16 (8)	5 (2)	5 (4)	31 (7)	nr	11 (10)
repaglinide/ metformin (PrandiMet) <sup>23</sup>	11 (11 both)	19 (7 metformin; 30 repaglinide)	nr	33 (0 metformin; 11 repaglinide)	nr	22 (11 metformin; 15 repaglinide)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported; URI = upper respiratory tract infection.

Adverse effects reported in the labeling for combination repaglinide/metformin (PrandiMet) reflect coadministration of repaglinide and metformin and was measured against monotherapy of metformin and repaglinide (Prandin).

***Special Populations***<sup>24,25,26</sup>

*Pediatrics*

Safety and efficacy of these products have not been established in pediatric patients. Their use is not recommended in children.

*Pregnancy*

All agents in this category are Pregnancy Category C.

*Renal Impairment*

No dosage adjustment of nateglinide is necessary in patients with mild to severe renal insufficiency.

All patients with severe renal impairment (creatinine clearance = 20-40 mL/min) should start repaglinide at 0.5 mg dose. Caution should be used in patients with creatinine clearance less than 20 mL/min and with those patients on hemodialysis.

The use of combination repaglinide/metformin (PrandiMet) is contraindicated in patients with renal impairment due to the metformin component.

*Hepatic Impairment*

Caution should be used with both agents in patients with moderate to severe hepatic impairment as there are very limited data in this patient population. Use longer intervals between doses with repaglinide in patients with hepatic impairment.

Due to metformin's association with lactic acidosis, combination repaglinide/metformin should not be used in patients with hepatic impairment.

*Ethnic groups*

A randomized, controlled, double-blind, double-dummy trial enrolled 230 Chinese patients with type 2 diabetes.<sup>27</sup> Patients were given repaglinide (Prandin) 1 mg three times daily or nateglinide (Starlix) 90 mg three times daily. After 12 weeks, there was no significant difference between the repaglinide and nateglinide groups in the effects of reducing fasting blood glucose ( $p>0.05$ ). Also, no significant difference was shown between the two groups in HbA<sub>1c</sub> ( $p>0.05$ ).

**Dosages**<sup>28,29,30</sup>

<b>Drug</b>	<b>Parameters</b>	<b>Dosage</b>	<b>Availability</b>
nateglinide (Starlix)	Initial therapy for patients near HbA <sub>1c</sub> goals (alone or in combination with metformin, pioglitazone, or rosiglitazone)	60 mg taken one to 30 minutes before each meal (three times daily)	60, 120 mg tablets
	Most patients (alone or in combination with metformin, pioglitazone, or rosiglitazone)	120 mg taken one to 30 minutes before each meal (three times daily)	
repaglinide (Prandin)	Initial therapy or HbA <sub>1c</sub> less than eight percent	0.5 mg taken zero to 30 minutes prior to each meal (2, 3, or 4 times daily)	0.5, 1, 2 mg tablets
	Previously treated with glucose-lowering drugs and HbA <sub>1c</sub> greater than or equal to eight percent	1 or 2 mg (and up to 4 mg) taken zero to 30 minutes prior to each meal (2, 3, or 4 times daily); maximum daily dose is 16 mg	
repaglinide/ metformin (PrandiMet)	Inadequately controlled with metformin monotherapy	Initiate dose at 1 mg/500 mg twice daily with meals, with gradual dose escalation based on glycemic response	1 mg/500 mg, 2 mg/500 mg tablets
	Inadequately controlled with meglitinide monotherapy	Initiate metformin component at 500 mg twice daily with meals	
	Current concomitant use of metformin and repaglinide	Initiate dose of repaglinide and metformin similar to, but not exceeding, current doses	

All agents within this category should be given within 15 minutes of a meal. If a patient skips a meal, the dose of that agent should also be skipped.

PrandiMet can be administered two to three times a day up to a maximum daily dose of 10 mg repaglinide/2,500 mg metformin. No more than 4 mg repaglinide/1,000 mg metformin should be taken per meal.

***Clinical Trials*****Search Strategies**

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all brand names in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the

investigation. Using these criteria, numerous studies were found. Data were further excluded based on the following characteristics: formulation or drug not available in U.S., single-blind or open-label design, or single-dose study. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Due to a paucity of double-blind, direct comparator trials, studies with an open-label design were included.

In countries outside of the US, blood glucose values are typically reported in mmol/L. For those studies reporting blood glucose values in mmol/L, the value in mg/dL can be estimated by multiplying the mmol/L value by 18.

#### nateglinide (Starlix) and glyburide (Diabeta<sup>®</sup>, Micronase<sup>®</sup>)

A study compared the effects of nateglinide, glyburide, and placebo on postmeal glucose excursions and insulin secretion in previously diet-treated patients with type 2 diabetes.<sup>31</sup> In the randomized, double-blind, placebo-controlled, multicenter study, patients received either nateglinide (120 mg before meals three times daily, n=51), glyburide (5 mg daily titrated to 10 mg daily after two weeks, n=50), or placebo (n=51), each given for eight weeks. Glucose, insulin, and C-peptide profiles during liquid meal challenges were measured at baseline and at eight weeks. Nineteen-point daytime glucose and insulin profiles, comprising three solid meals, were measured at weeks one and seven. During the liquid-meal challenge, nateglinide reduced the incremental glucose area under the curve (AUC) more effectively than glyburide (-88.9 versus -48.8 mg·h/dL, respectively, p<0.05). Glyburide reduced fasting plasma glucose (FPG) more effectively than nateglinide (-52 versus -18 mg/dL, respectively, p<0.001). C-peptide induced by glyburide was greater than that induced by nateglinide (+1.83 versus +0.95 nmol·h/l, p<0.01), and only glyburide increased fasting insulin levels. During the solid meal challenges, nateglinide and glyburide elicited similar overall glucose control (12-hour incremental AUC = -237 versus -275 mg·h/dL).

A randomized, multicenter, double-masked, two-year study of 428 drug-naive patients with type 2 diabetes measured primary variable, HbA<sub>1c</sub>, and secondary variables, FPG, body weight, and postprandial glucose excursions (PPGEs) during oral glucose tolerance tests.<sup>32</sup> Patients received nateglinide 120 mg before meals or glyburide 1.25 mg daily (before breakfast) plus open-label metformin 500 mg daily (before evening meal) for the initial four weeks. During a subsequent 12-week titration period, glyburide and metformin were increased by 1.25 mg and 500 mg increments to maximum daily doses of 10 mg and 2,000 mg, respectively. In nateglinide/metformin-treated patients, mean HbA<sub>1c</sub> was 8.4 percent at baseline and 6.9 percent at week 104. In glyburide/metformin-treated patients, mean HbA<sub>1c</sub> was 8.3 percent at baseline and 6.8 percent at week 104 (p=NS between treatments). The change in FPG was -1.6 (p<0.0001) and -2.4 mmol/L (p<0.0001) in patients receiving nateglinide/metformin and glyburide/metformin, respectively (p<0.01 between groups). The change in PPGE averaged -96 (p<0.0001) and -57 mmol·l<sup>-1</sup>·min<sup>-1</sup> (p<0.05) in patients receiving nateglinide/metformin and glyburide/metformin, respectively. The two treatments achieved similar efficacy with differential effects on FPG versus PPGEs. Body weight decreased slightly in patients randomized to the nateglinide/metformin group (-0.4 kg, p=0.8143) and increased slightly in patients in the glyburide/metformin group (+0.8 kg, p=0.0011). The change in body weight was only statistically significant relative to baseline for the glyburide/metformin group, but the between-group

difference was statistically significant ( $p=0.0115$ ). Hypoglycemia occurred in 8.2 and 17.7 percent of patients receiving nateglinide/metformin and glyburide/metformin, respectively.

nateglinide (Starlix) and metformin (Glucophage®)

In a randomized, double-blind trial, type 2 diabetic patients with HbA<sub>1c</sub> levels between 6.8 and 11 percent were given nateglinide 120 mg before meals ( $n=179$ ), metformin 500 mg three times daily ( $n=178$ ), combination therapy ( $n=172$ ), or placebo ( $n=172$ ) for 24 weeks.<sup>33</sup> HbA<sub>1c</sub> (nateglinide -0.5 percent, metformin -0.8 percent) and FPG (nateglinide -0.7 mmol/L, metformin -1.6 mmol/L;  $p\leq 0.0001$ ) were significantly lower in the treatment groups but increased in the placebo group (+0.5 percent for HbA<sub>1c</sub> and +0.4 mmol/L for FPG; both  $p\leq 0.0001$ ). Combination therapy provided an additive response compared to monotherapy (HbA<sub>1c</sub> -1.4 percent, FPG -2.4 mmol/L;  $p\leq 0.01$ ). The reduction in mealtime glucose was greater with nateglinide monotherapy and combination therapy compared with metformin monotherapy or placebo (adjusted AUC<sub>0-130min</sub> -2.1, -2.5, -1.1, and -0.6 mmol·h<sup>-1</sup>·h<sup>-1</sup>;  $p\leq 0.0001$  nateglinide and combination versus metformin and placebo). Postprandial hyperglycemia was more improved in the nateglinide group. There were no significant changes in body weight in any of the active treatment groups. All regimens were well tolerated.

A multicenter, double-blind, parallel-group trial evaluated the addition of nateglinide in 467 type 2 diabetes patients stabilized on high-dose metformin.<sup>34</sup> Metformin-treated patients with HbA<sub>1c</sub> between 6.8 and 11 percent were randomized to add nateglinide 60 mg, 120 mg, or placebo before three meals daily to metformin 1,000 mg twice daily for 24 weeks. HbA<sub>1c</sub> was significantly reduced with nateglinide 60 mg and 120 mg plus metformin compared with metformin control (-0.36 percent,  $p=0.003$ ; -0.59 percent,  $p<0.001$  respectively). Greater benefits occurred if patients had elevated HbA<sub>1c</sub> at baseline (-1.38 percent with nateglinide 120 mg in patients with HbA<sub>1c</sub>>9.5 percent). A modest reduction in FPG was observed. Events suggestive of hypoglycemia were confirmed in 1.1 percent of cases. Most symptoms suggestive of hypoglycemia occurred in patients with lower HbA<sub>1c</sub> levels ( $\leq$  eight percent) at baseline, although no confirmed cases of hypoglycemia occurred with nateglinide 60 mg in this patient group. Weight gain over 24 weeks was 0.9 kg with nateglinide 120 mg versus metformin alone, and plasma lipids remained unchanged. The combination of these agents was well tolerated.

nateglinide (Starlix) and rosiglitazone (Avandia®)

In the 24-week, multicenter, double-blind trial, 402 patients with HbA<sub>1c</sub> between seven and 11 percent were randomized to receive nateglinide 120 mg before meals and rosiglitazone 8 mg daily or placebo plus rosiglitazone 8 mg daily.<sup>35</sup> Efficacy parameters tested included HbA<sub>1c</sub> and plasma glucose and insulin levels in the fasting state and after a standardized meal challenge. In patients randomized to nateglinide, HbA<sub>1c</sub> values decreased from 8.3 to 7.5 percent ( $p<0.0001$  versus placebo). Additionally, FPG levels decreased (-0.7 mmol/L), two-hour postprandial glucose levels decreased (-2.7 mmol/L), and 30-minute insulin levels increased (+165 pmol/L) in the group treated with nateglinide ( $p<0.001$ ). There were no statistically significant changes reported for any values for the placebo group. Body weight increased significantly in both groups (combination therapy +3.1 kg, monotherapy +1.1 kg;  $p<0.0001$ ).

repaglinide (Prandin) and nateglinide (Starlix)

The efficacy and safety of repaglinide monotherapy and nateglinide monotherapy in type 2 diabetic patients previously treated with diet and exercise were compared in a randomized, parallel-group, open-label, multicenter trial.<sup>36</sup> Patients ( $n=150$ ) were randomized to receive either repaglinide 0.5 mg/meal (up to a maximum dose of 4 mg/meal) or nateglinide 60 mg/meal



(up to a maximum dose of 120 mg/meal) for 16 weeks. Outcomes examined were the change in HbA<sub>1c</sub> and FPG from baseline as well as the incidence of adverse drug effects and episodes of hypoglycemia. Patients in the repaglinide treatment group had a significantly greater reduction in HbA<sub>1c</sub> (-1.57 versus -1.04;  $p \leq 0.002$ ) and FPG levels (-57 versus -18 mg/dL;  $p < 0.001$ ) from baseline compared to those patients treated with nateglinide. Seven percent of subjects treated with repaglinide had minor hypoglycemic episodes (blood glucose  $< 50$  mg/dL) versus zero patients for nateglinide. Mean weight gain at the end of the study was 1.8 kg in the repaglinide group as compared with 0.7 kg for the nateglinide group. The safety profile of both treatment groups was found to be comparable.

An open-label, parallel-group, randomized, multicenter trial of 192 patients sought to compare the efficacy and safety of repaglinide versus nateglinide when used in a combination regimen with metformin for the treatment of type 2 diabetes.<sup>37</sup> Patients had a HbA<sub>1c</sub> between seven and twelve percent and had been previously treated with metformin or a sulfonylurea. After four weeks of run-in therapy with metformin, patients were randomized to receive either repaglinide 1 mg/meal (up to 4 mg/meal) or nateglinide 120 mg/meal (with an optional reduction to 60 mg/meal if needed) for a 16-week period. The primary efficacy endpoints were final HbA<sub>1c</sub> and the change in HbA<sub>1c</sub> from baseline. Secondary endpoints included FPG levels. Final HbA<sub>1c</sub> was lower for patients treated with repaglinide/metformin (7.1 percent versus 7.5 percent). Patients who were treated with repaglinide/metformin also had a significantly greater reduction in HbA<sub>1c</sub> from baseline (-1.28 versus -0.67;  $p < 0.001$ ) as well as a significantly greater reduction in FPG (-39 versus -21 mg/dL). Safety assessments between the two treatment groups were comparable.

#### repaglinide (Prandin) and metformin (Glucophage®)

In a multicenter double-blind trial, 83 type 2 diabetic patients with inadequate glycemic control (HbA<sub>1c</sub>  $> 7.1$  percent) on metformin were randomized to receive add-on repaglinide ( $n=27$ ), repaglinide monotherapy ( $n=29$ ), or to continue on metformin monotherapy ( $n=27$ ).<sup>38</sup> The repaglinide dose was titrated for four to eight weeks, followed by a three-month dose maintenance period. In subjects receiving combination therapy, there was a significant reduction in both HbA<sub>1c</sub> (8.3 to 6.9 percent;  $p=0.0016$ ) and FPG (by 2.2 mmol/L;  $p=0.0003$ ). There were no significant changes observed in HbA<sub>1c</sub> or FPG levels in either repaglinide or metformin monotherapy treatment groups. Patients treated with repaglinide (monotherapy and combination group) experienced a significant increase in body weight (2.4 and 3.0 kg, respectively).

#### repaglinide (Prandin) and glipizide (Glucotrol®)

To evaluate the long-term effectiveness and safety of repaglinide, 256 type 2 diabetics without signs of severe microvascular or macrovascular complications were included in the double-blind, multicenter, parallel-group, comparative trial.<sup>39</sup> Patients were randomized to repaglinide, 1 to 4 mg at mealtimes or glipizide 5 to 15 mg daily. Changes in FBG and HbA<sub>1c</sub> during the 12 months of treatment showed a significant difference in favor of repaglinide. In oral hypoglycemic agent-naïve patients, HbA<sub>1c</sub> decreased in the repaglinide and glipizide groups by 1.5 and 0.3 percent, respectively ( $p < 0.05$  between groups). In addition, FBG decreased significantly in the repaglinide group compared with the glipizide group (2.4 versus 1.0 mmol/L, respectively;  $p < 0.05$ ). No patients in either group experienced a major hypoglycemic event, and the number of patients experiencing minor hypoglycemia was similar in the repaglinide and glipizide groups (15 and 19 percent, respectively).

repaglinide (Prandin) and glyburide (Diabeta, Micronase)

Repaglinide was compared to glyburide in a one-year, randomized, double-blind, parallel group multicenter study in type 2 diabetics.<sup>40</sup> Patients were given repaglinide (n=383) or glyburide (n=193), and doses were titrated to achieve a FPG of 80 to 140 mg/dL over eight weeks and then continued for one year. Repaglinide provided similar glycemic control as glyburide as measured by HbA<sub>1c</sub> and FPG over the one-year study period. Safety and lipid panel changes were similar in both groups. Weight gain was reported to be less in the treatment-naïve patients receiving repaglinide.

repaglinide (Prandin) and glimepiride (Amaryl®)

The randomized, placebo-controlled, double-blind trial was conducted at a single center in Italy.<sup>41</sup> Patients were randomized to receive repaglinide or glimepiride. The dose of study drug was optimized over an eight-week titration period followed by a 12-month treatment period. One hundred twenty-four patients (63 women, 61 men) completed the study, 62 in each treatment group. After six and 12 months of treatment, FPG levels and HbA<sub>1c</sub> values were significantly reduced from baseline in both groups. In this population of patients with type 2 diabetes, repaglinide and glimepiride improved glycemic control and reduced levels of other metabolic parameters known to be cardiovascular risk factors—lipoprotein (a), plasminogen activator inhibitor-1, and homocysteine.

Meta-Analyses

Several databases were searched, including The Cochrane Library, MEDLINE, EMBASE, ongoing trials databases, and the American Diabetes Association and European Association for the Study of Diabetes websites.<sup>42</sup> Randomized, controlled, parallel or cross-over trials comparing at least 10 weeks of meglitinide use to placebo, other meglitinides, metformin, or in combination with insulin were included. Fifteen trials involving 3,781 participants were included. In the eleven studies comparing meglitinides to placebo, both repaglinide (Prandin) and nateglinide (Starlix) resulted in reductions in HbA<sub>1c</sub> (0.1 to 2.1 percent reduction in HbA<sub>1c</sub> for repaglinide; 0.2 to 0.6 percent for nateglinide). Only two trials compared repaglinide to nateglinide (342 total participants), with greater reduction in HbA<sub>1c</sub> in those receiving repaglinide. In comparisons with metformin, weight gain was generally greater, diarrhea less frequent, and hypoglycemia more frequent in those treated with meglitinides.

**Summary**

The meglitinides provide an additional treatment option for select patients who have failed to achieve glycemic goals with other oral antidiabetic agents. Although the 2009 update to the ADA consensus algorithm continues not to recommend this class of medication as part of the treatment algorithm, the meglitinides have been shown to control postprandial hyperglycemia in type 2 diabetic patients and lower HbA<sub>1c</sub>. Despite having relatively similar indications and adverse effects, the ADA cites repaglinide (Prandin) as being somewhat more effective than nateglinide (Starlix). Directly comparative data of good quality are not available.

Repaglinide/metformin (PrandiMet) is available for patients who require multiple agents for treatment of type 2 diabetes.

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## References

- <sup>1</sup> Starlix [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; July 2008.
- <sup>2</sup> Prandin [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2006.
- <sup>3</sup> PrandiMet [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2008.
- <sup>4</sup> <http://diabetes.niddk.nih.gov/dm/pubs/statistics>. Accessed February 11, 2010.
- <sup>5</sup> National Institute of Diabetes and Digestive and Kidney Diseases. National Diabetes Statistics, 2007 fact sheet. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, 2007.
- <sup>6</sup> Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. *Diabetes Care*. 2009; 32(1):193-203.
- <sup>7</sup> Starlix [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; July 2008.
- <sup>8</sup> Prandin [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2006.
- <sup>9</sup> PrandiMet [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2008.
- <sup>10</sup> Glucophage/Glucophage XR [package insert]. Princeton, NJ; Bristol-Myers Squibb; January 2009.
- <sup>11</sup> Weaver ML, Orwig BA, Rodriguez LC, et al. Pharmacokinetics and metabolism of nateglinide in humans. *Drug Metab Dispos*. 2001; 29(4 Pt 1):415-421.
- <sup>12</sup> Starlix [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; July 2008.
- <sup>13</sup> Prandin [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2006.
- <sup>14</sup> Starlix [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; July 2008.
- <sup>15</sup> Prandin [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2006. Accessed at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/020741s035lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020741s035lbl.pdf)
- <sup>16</sup> PrandiMet [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2008.
- <sup>17</sup> Glucophage/Glucophage XR [package insert]. Princeton, NJ; Bristol-Myers Squibb; January 2009.
- <sup>18</sup> Starlix [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; July 2008.
- <sup>19</sup> Prandin [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2006.
- <sup>20</sup> PrandiMet [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2008.
- <sup>21</sup> Starlix [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; July 2008.
- <sup>22</sup> Prandin [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2006.
- <sup>23</sup> PrandiMet [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2008.
- <sup>24</sup> Starlix [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; July 2008.
- <sup>25</sup> Prandin [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2006.
- <sup>26</sup> PrandiMet [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2008.
- <sup>27</sup> Li J, Tian H, Li Q, et al. Improvement of insulin sensitivity and beta-cell function by nateglinide and repaglinide in type 2 diabetic patients - a randomized controlled double-blind and double-dummy multicentre clinical trial. *Diabetes Obes Metab*. 2007; 9(4):558-565.
- <sup>28</sup> Starlix [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; July 2008.
- <sup>29</sup> Prandin [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2006.
- <sup>30</sup> PrandiMet [package insert]. Princeton, NJ; Novo Nordisk Inc.; June 2008.
- <sup>31</sup> Hollander PA, Schwartz SL, Gatlin MR, et al. Importance of early insulin secretion: comparison of nateglinide and glyburide in previously diet-treated patients with type 2 diabetes. *Diabetes Care*. 2001; 24(6):983-988.
- <sup>32</sup> Gerich J, Raskin P, Jean-Louis L, et al. PRESERVE-beta: two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin. *Diabetes Care*. 2005; 28(9):2093-2099.
- <sup>33</sup> Horton ES, Clinkingbeard C, Gatlin M, et al. Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care*. 2000; 23(11):1660-1665.
- <sup>34</sup> Marre M, Van Gaal L, Usadel KH, et al. Nateglinide improves glycaemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. *Diabetes Obes Metab*. 2002; 4(3):177-186.
- <sup>35</sup> Fonseca V, Grunberger G, Gupta S, et al. Addition of nateglinide to rosiglitazone monotherapy suppresses mealtime hyperglycemia and improves overall glycemic control. *Diabetes Care*. 2003; 26(6):1685-1690.
- <sup>36</sup> Rosenstock J, Hassman DR, Maddor RD, et al. Repaglinide versus nateglinide monotherapy: a randomized, multicenter study. *Diabetes Care*. 2004; 27(6):1265-1270.
- <sup>37</sup> Raskin P, Klaff L, McGill J, et al. Efficacy and safety of combination therapy: repaglinide plus metformin versus nateglinide plus metformin. *Diabetes Care*. 2003; 26(7):2063-2068.
- <sup>38</sup> Moses R, Solobodniuk R, Boyages S, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 1999; 22(1):119-124.
- <sup>39</sup> Madsbad S, Kilhøvd B, Lager I, et al. Comparison between repaglinide and glipizide in Type 2 diabetes mellitus: a 1-year multicentre study. *Diabet Med*. 2001; 18(5):395-401.
- <sup>40</sup> Marbury T, Huang WC, Strange P, et al. Repaglinide versus glyburide: a one-year comparison trial. *Diabetes Res Clin Prac*. 1999; 43(3):155-166.
- <sup>41</sup> Derosa G, Mugellini A, Ciccarelli L, et al. Comparison between repaglinide and glimepiride in patients with type 2 diabetes mellitus: a one-year, randomized, double-blind assessment of metabolic parameters and cardiovascular risk factors. *Clin Ther*. 2003; 25(2):472-484.
- <sup>42</sup> Black C, Donnelly P, McIntyre L, et al. Meglitinide analogues for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2007; (2):CD004654.