Therapeutic Class Overview
Meglitinides

INTRODUCTION

- Diabetes mellitus affects more than 30 million people in the United States. More than 84 million American adults have prediabetes, with 90% of this population unaware that they have the condition (*Centers for Disease Control and Prevention [CDC] 2018*).
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes, and is characterized by elevated fasting and postprandial glucose concentrations. It is a chronic illness that requires continuing medical care and ongoing patient self-management, education and support to prevent acute complications and to reduce the risk of long-term complications (*American Diabetes Association [ADA] 2019, CDC 2018*).
- Complications of T2DM include heart disease, stroke, vision loss, kidney disease, and lower-limb amputations. It is the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness and the seventh leading cause of death in the United States (*CDC 2018*).
- Medical costs for patients with diabetes are double the costs for patients without diabetes (*CDC 2018*).
- Classes of oral medications for the management of blood glucose levels in patients with T2DM may exert their effects through various mechanisms, including decreasing hepatic glucose production, increasing insulin secretion, increasing insulin sensitivity, decreasing the rate of carbohydrate absorption, decreasing glucagon secretion, and blocking glucose reabsorption by the kidney (*Davies et al 2018*).
- Key pharmacologic options for T2DM include sulfonylureas, biguanides, thiazolidinediones (TZDs), meglitinides (or glinides), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and insulin (*Davies et al 2018*). Many patients with T2DM will require combination therapy (*Garber et al 2018*).
- Meglitinides are rapid-acting oral antidiabetic agents that lower blood glucose levels by stimulating insulin secretion from the pancreas in a beta-cell dependent manner. They are structurally unrelated to the oral sulfonylurea insulin secretagogues.
- This review will focus on the 2 approved meglitinides, repaglinide and nateglinide. Repaglinide is also Food and Drug Administration (FDA)-approved as a combination product with metformin.
- Medispan class: Endocrine and Metabolic Drugs; Meglitinide Analogues; Meglitinide-Biguanide Combination

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Starlix (nateglinide)	✔
Prandin (repaglinide)	✔
Prandimet (repaglinide/metformin)*	✔ *

*The brand product, Prandimet, is no longer marketed. Additionally, generic repaglinide/metformin has experienced a long-term backorder and may not be available.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication*	**Starlix** (nateglinide)	**Prandin** (repaglinide)	**Prandimet** (repaglinide/ metformin)
Adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔	✔	
Combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM who are already treated with a meglitinide and metformin or who have inadequate glycemic control on a meglitinide alone or metformin alone			✔

*Limitation of use: not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis

(Prescribing information: Prandimet 2017, Prandin 2019, Starlix 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The effectiveness of repaglinide and nateglinide as monotherapy and in combination with other oral antidiabetic agents has been demonstrated in numerous clinical trials. Meglitinides have been compared to other antidiabetic agents including sulfonylureas, metformin, and insulin (*Bellomo et al 2011, Cesur et al 2007, Derosa et al 2003, Fang et al 2014, Hollander et al 2003, Omori et al 2018, Ozbek et al 2006, Wolffenbuttel et al 1999*). There were at least 3 studies comparing repaglinide to nateglinide head-to-head (*Li J et al 2007, Raskin et al 2003, Rosenstock et al 2004*). The meglitinides were used as monotherapy in *Rosenstock et al* and in combination with metformin in *Raskin et al*.
  - In the monotherapy trial comparing repaglinide to nateglinide (N = 150), a clinically significant reduction in hemoglobin A1c (HbA1c) was seen in both groups with a mean reduction of 1.6% in those randomized to repaglinide vs 1% in those randomized to nateglinide (p = 0.002) (*Rosenstock et al 2004*). At the end of the study, 54% of the repaglinide-treated patients had HbA1c values less than 7% vs 42% of the nateglinide-treated patients; however, the difference did not reach statistical significance (p = 0.18). There were no major hypoglycemic episodes in either treatment group. Patients receiving repaglinide experienced more weight gain than those receiving nateglinide (1.8 kg vs 0.7 kg; p = 0.04).
  - In the second study comparing repaglinide to nateglinide (N = 192), both in combination with metformin, a clinically significant reduction in HbA1c was seen in both groups with the greatest reduction in the repaglinide group (1.3 vs 0.7%, respectively; p < 0.001). The percent of patients who achieved final HbA1c values of less than 7% was 59% for the repaglinide group and 47% for the nateglinide group (p value not reported). Mean changes in fasting plasma glucose were significantly greater for patients receiving repaglinide than nateglinide (p = 0.002) (*Raskin et al 2003*).
  - In a Chinese study, both repaglinide and nateglinide had similar effects on fasting blood glucose and postprandial glucose (p > 0.05) (*Li J et al 2007*).
- A meta-analysis of 4 clinical trials in Chinese patients (N = 955) found that nateglinide and repaglinide had similar reductions in HbA1c and fasting blood glucose and had similar adverse events (*Li C et al 2009*).
- A multicenter, open-label, randomized trial, conducted in Japan, enrolled 57 lean elderly patients with T2DM who were being treated with a sulfonylurea. Patients were randomized to switch to repaglinide or continue on the sulfonylurea for 12 weeks. Patients switching to repaglinide had comparable HbA1c levels to those remaining on a sulfonylurea (-0.07% and +0.02%, respectively; p = 0.37). There was also no significant difference in the number of hypoglycemic episodes (*Omori et al 2018*).
- Additionally, monotherapy with repaglinide was compared to metformin in patients with newly diagnosed T2DM who were naïve to oral antihyperglycemic agents. Repaglinide and metformin achieved comparable results in reduction of HbA1c, fasting plasma glucose and post-prandial glucose (*Fang et al 2014*).
- In a double-blind, placebo-controlled trial, 289 patients were randomized to nateglinide 30 mg, 60 mg, 120 mg, 180 mg, or placebo for 12 weeks. Increased insulin secretion was observed with maximal values seen at 30 minutes and a return to normal values in 3 to 4 hours. HbA1c values were compared between baseline and 12 weeks, and significant reductions were seen for the 60 mg, 120 mg, and 180 mg doses in the range of 0.45% to 0.64% (*Hanefeld et al 2000*).
- Additional studies have demonstrated that when nateglinide or repaglinide was added to metformin therapy, the changes from baseline for HbA1c and fasting plasma glucose levels for either combination were significantly greater than either meglitinide monotherapy or metformin monotherapy (*Black et al 2007, Horton et al 2000, Marre et al 2002, Moses et al 1999).* This additive effect was also seen when repaglinide was given with rosiglitazone (*Raskin et al 2004*). The change in HbA1c and fasting plasma glucose from baseline was significant for repaglinide plus rosiglitazone when compared to either as monotherapy.
- In a systematic review of 136 trials, results from clinical trials showed that most oral agents, including TZDs, metformin, and repaglinide, improved glycemic control to the same degree as sulfonylureas (absolute decrease in HbA1c level of about 1%) (moderate-to-high strength of evidence) (*Bolen et al 2007*). Nateglinide and alpha-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials (low strength of evidence). TZDs were the only class with a beneficial effect on high-density lipoprotein (HDL) levels (mean relative increase, 3 to 5 mg/dL) but a harmful effect on low-density lipoprotein (LDL) levels (mean relative increase, 10 mg/dL) compared with

other oral agents. Metformin decreased LDL levels by about 10 mg/dL, whereas other oral agents had no effects on LDL (moderate strength of evidence). TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on systolic blood pressure (moderate strength of evidence). Most agents except metformin increased body weight by 1 to 5 kg (moderate strength of evidence).

- A network meta-analysis was conducted to determine whether the addition of various antidiabetic drug regimens to metformin monotherapy in patients with T2DM led to significant reductions in HbA1c. All agents reduced HbA1c more than placebo but at varying levels. Insulin glargine, sulfonylureas, and nateglinide were associated with increased hypoglycemia risk when compared to placebo, but repaglinide, GLP-1 receptor agonists, DPP-4 inhibitors, and TZDs were not (*Mearns et al 2015*).
- According to studies comparing the efficacy of a meglitinide to other oral diabetic agents, meglitinides may offer an alternative to be used when side effects of other oral agents are intolerable or when those agents are contraindicated. From the data presented, there is no evidence available to indicate what effects meglitinides will have on important long-term outcomes, and it is difficult to determine if one meglitinide offers an advantage in glycemic control or safety over the other.

CLINICAL GUIDELINES

- Current guidelines recommend that metformin, along with lifestyle intervention, should be the initial pharmacologic therapy for T2DM in the absence of specific contraindications.
  - According to the ADA and a joint consensus report from the ADA and the European Association for the Study of Diabetes (EASD), dual therapy or triple therapy can be considered in patients not achieving their HbA1c goal on metformin monotherapy (*ADA 2019, Davies et al 2018*). Choice of add-on therapy should be determined based on 1) whether the patient has established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD); and 2) whether there is a compelling need to minimize hypoglycemia or a compelling need to minimize weight gain or promote weight loss in patients without established ASCVD or CKD.
    - If ASCVD predominates, a GLP-1 receptor agonist with proven cardiovascular disease (CVD) benefit or an SGLT2 inhibitor with proven CVD benefit (if estimated glomerular filtration rate [eGFR] is adequate) is recommended.
    - If heart failure or CKD predominates, an SGLT2 inhibitor with evidence of reducing heart failure and/or CKD progression is preferred if the eGFR is adequate. If the SGLT2 inhibitor is not tolerated or contraindicated, or if the eGFR is less than adequate, a GLP-1 receptor agonist with proven CVD benefit is recommended.
    - In patients without established ASCVD or CKD:
      - If there is a compelling need to minimize hypoglycemia, recommendations include a DPP-4 inhibitor, a GLP-1 receptor agonist, an SGLT2 inhibitor, or a TZD.
      - If there is a compelling need to minimize weight gain or promote weight loss, a GLP-1 receptor agonist with good efficacy for weight loss or an SGLT2 inhibitor is recommended.
    - The early introduction of basal insulin is a well-established approach to treatment in patients who have very high HbA1c levels (> 11%), symptoms of hyperglycemia, or evidence of ongoing catabolism (eg, weight loss) (*Davies et al 2018*).
    - In most patients who need the greater glucose-lowering effect of an injectable medication (ie, HbA1c is above target despite dual/triple therapy), GLP-1 receptor agonists are preferred to insulin.
    - Meglitinides are not used commonly in the United States (*Davies et al 2018*). Advantages of these products include a reduction in postprandial glucose excursions, dosing flexibility, and safe use in advanced renal disease with cautious dosing (especially repaglinide). Disadvantages include a risk of hypoglycemia, weight gain, frequent dosing schedule, and uncertain cardiovascular safety.
  - According to the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE), the choice of diabetic therapies must be individualized based on attributes specific to the patient and the medication (*Garber et al 2018*). Metformin is recommended as the preferred initial agent for monotherapy in patients with an entry HbA1c < 7.5%; however, monotherapy with other agents may be considered. Combination therapies including metformin plus 1 or 2 additional agents are recommended for patients with an entry HbA1c ≥ 7.5%. Several options for dual- and triple-therapy are presented in a hierarchy, with GLP-1 receptor agonists and SGLT2 inhibitors listed as the top 2 options to be added. In patients with an entry HbA1c > 9%, dual- or triple therapy should be considered if patients are asymptomatic, and insulin considered if patients are symptomatic (*Garber et al 2018*).

- Meglitinides have somewhat lower HbA1c-lowering effects and a shorter half-life, and therefore have a lower risk of prolonged hypoglycemia compared to sulfonylureas. Meglitidines are not generally preferred as monotherapy, but may be appropriate for select patients.

SAFETY SUMMARY

- Contraindications:
  - Hypersensitivity to the drug or any of its ingredients
  - Concomitant use with gemfibrozil: repaglinide and repaglinide/metformin
  - Severe renal impairment (eGFR < 30 mL/min/1.73 m^2): repaglinide/metformin
  - Acute or chronic metabolic acidosis, including diabetic ketoacidosis: repaglinide/metformin
- Boxed warning – repaglinide/metformin:
  - Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, concomitant use of certain drugs (eg, carbonic anhydrase inhibitors such as topiramate), excessive alcohol intake, age ≥ 65 years, hepatic impairment, and hypoxic states (eg, acute congestive heart failure).
  - If lactic acidosis is suspected, repaglinide/metformin should be discontinued and the patient hospitalized immediately. Prompt hemodialysis is recommended.
- Warnings/Precautions:
  - Hypoglycemia
  - No clinical studies have conclusively established evidence of macrovascular risk reduction with therapy.
  - Repaglinide and repaglinide/metformin should not be used with NPH insulin (risk of serious cardiovascular adverse reactions).
  - See prescribing information for other warnings for repaglinide/metformin due to its metformin component.
- Adverse Effects:
  - The most common adverse effects for the class include hypoglycemia, headache, nausea, dyspepsia, back pain, diarrhea, upper respiratory tract infection, flu symptoms, dizziness, sinusitis, and arthropathy/arthralgia.
- Drug Interactions:
  - Repaglinide
    - Cyclosporine, gemfibrozil, clopidogrel, cytochrome P450 (CYP) 2C8 inhibitors (eg, trimethoprim, gemfibrozil, montelukast, clopidogrel), and CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, erythromycin) may increase the plasma concentrations of repaglinide.
    - Drugs that induce CYP3A4 and/or CYP2C8 enzyme systems (eg, rifampin, barbiturates, and carbamazepine) may reduce the glucose-lowering effect of repaglinide.
  - Nateglinide
    - Nonsteroidal anti-inflammatory drugs, salicylates, monoamine oxidase inhibitors, non-selective beta-adrenergic-blocking agents, anabolic hormones, guanethidine, and CYP2C9 inhibitors (eg, fluconazole, voriconazole, amiodarone) may increase the glucose-lowering action of nateglinide and increase susceptibility to hypoglycemia.
    - Thiazides, corticosteroids, thyroid products, sympathomimetics, somatropin, somatostatin analogues, and CYP inducers (eg, rifampin, phenytoin, St. John's Wort) may reduce the hypoglycemic action of nateglinide and increase susceptibility to hyperglycemia.
  - This section is not a comprehensive list of potential drug interactions. See prescribing information for additional products that may increase the risk of hypoglycemia or decrease the blood glucose lowering effect of the meglitinides as well as drug interactions based on the metformin component of repaglinide/metformin.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Starlix (nateglinide)	Tablets	Oral	3 times daily	Should be taken up to 30 minutes prior to meals. If a meal is skipped, the scheduled dose should be skipped to reduce the risk of hypoglycemia.
Prandin (repaglinide)	Tablets	Oral	2 to 4 times daily (max daily dose: 16 mg)	Should be taken within 30 minutes of a meal. If a meal is skipped, the scheduled dose should be skipped to reduce the risk of hypoglycemia. In severe renal impairment (creatinine clearance 20 to 40 mL/min), should be initiated at a low dose (0.5 mg) and gradually titrated.
Prandimet (repaglinide/ metformin)	Tablets	Oral	2 to 3 times daily (max dose: 10/2500 mg daily or 4/1000 mg per meal)	Should be taken within 15 to 30 minutes of a meal. If a meal is skipped, the scheduled dose should be skipped to reduce the risk of hypoglycemia. In patients inadequately controlled with metformin, the recommended starting dose of repaglinide/metformin is 1/500 mg administered twice daily. In patients inadequately controlled with meglitinide monotherapy, the recommended starting dose of the metformin component is 500 mg twice daily. If eGFR < 30 mL/min/1.73 m^2, repaglinide/metformin is contraindicated and should be discontinued. The combination should not be initiated in patients with eGFR between 30 to 45 mL/min/1.73 m^2. If eGFR falls below 45 mL/min/1.73 m^2, the benefits and risks of continuing therapy should be assessed; if eGFR falls below 30 mL/min/1.73 m^2, the combination should be discontinued.

CONCLUSION

- The meglitinides are a class of oral antidiabetic agents that increase insulin secretion in the pancreas. They are FDA approved as an adjunct to diet and exercise either alone or in combination with other therapies for the treatment of T2DM.
- The pharmacokinetic and pharmacodynamic properties of this drug class suggest they have the potential to produce a rapid, short-lived insulin secretory response.
- The effectiveness of these agents as monotherapy and in combination with other oral antidiabetic agents has been demonstrated in a number of clinical trials. In studies comparing meglitinides to placebo, repaglinide and nateglinide resulted in reductions in HbA1c of 0.1% to 2.1% and 0.2% to 0.6%, respectively. Combination studies with metformin demonstrated that combined therapy produced clinically (and statistically) significant reductions in HbA1c compared with metformin alone without any reported severe hypoglycemia or other adverse events, but at the expense of a statistically significant weight gain (repaglinide and metformin) (*Black et al 2007*).
- Head-to-head clinical trials comparing the efficacy of repaglinide to nateglinide are limited. In one study, a clinically significant reduction in HbA1c was seen in those randomized to repaglinide (1.6%) compared to those randomized to nateglinide (1%). However, the proportion of patients achieving an HbA1c < 7% did not differ between treatment groups. There were no major hypoglycemic episodes in either treatment group. In another study comparing repaglinide to

nateglinide, both in combination with metformin, a clinically significant reduction in HbA1c was seen in both groups with the greatest reduction in the repaglinide group (1.3% vs 0.7%, respectively; p < 0.001) (*Raskin et al 2003*).

- Based on studies comparing the efficacy of a meglitinide to other oral diabetic agents, meglitinides may be considered alternative oral antihyperglycemic agents of similar potency to metformin and sulfonylureas, and can be used where side effects of the other oral diabetic agents are intolerable or where those agents are contraindicated. There is no evidence available to indicate what effects meglitinides will have on important long-term outcomes, and it is difficult to determine if one meglitinide offers an advantage in glycemic control or safety over the other.
- Adverse events associated with meglitinides include hypoglycemia, headache, nausea, dyspepsia, back pain, diarrhea, upper respiratory tract infection, flu symptoms, dizziness, sinusitis, and arthropathy/arthralgia.
- Current guidelines recommend that metformin, along with lifestyle intervention, should be the initial pharmacologic therapy for T2DM in the absence of specific contraindications (*ADA 2019, Garber et al 2018, Davies et al 2018*). Meglitinides are listed as one of several potential alternatives or add-on therapies; however, other classes are generally preferred in combination with metformin as dual or triple combination therapy for patients with T2DM (*ADA 2018, Davies et al 2018*). According to a joint consensus report by the ADA and EASD, advantages of meglitinides include a reduction in postprandial glucose excursions, dosing flexibility, and safe use in advanced renal disease with cautious dosing (especially repaglinide) (*Davies et al 2018*). Disadvantages include a risk of hypoglycemia, weight gain, frequent dosing schedule, and uncertain cardiovascular safety.
- The 2018 AACE/ACE guidelines note that the meglitinides have somewhat lower HbA1c-lowering effects and shorter half-lives, and thus a lower risk of prolonged hypoglycemia, relative to sulfonylureas (*Garber et al 2018*).

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