Hypoglycemics, Meglitinides
Therapeutic Class Review (TCR)

January 10, 2018

Please Note: This clinical document has been retired. It can be used as a historical reference.

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
nateglinide (Starlix®)[1]	generic, Novartis	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).
repaglinide (Prandin®)[2]	generic, Novo Nordisk, Gemini	Adjunct to diet and exercise in patients with T2DM who cannot be controlled by diet and exercise alone.
repaglinide/ metformin[3]	generic	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.

OVERVIEW

Diabetes was the seventh leading cause of death in the United States (U.S.) in 2015 and most likely is an under reported cause of death.[4] It is estimated that 30.3 million people in the U.S. have diabetes. In adults, type 2 diabetes mellitus (T2DM) accounts for about 90% to 95% of all diagnosed cases of diabetes. Improved glycemic control benefits patients with either type 1 or type 2 diabetes. In addition to exogenous insulin, there are several pathways by which blood glucose is regulated in diabetic patients. The meglitinides, nateglinide (e.g., Starlix) and repaglinide (e.g., Prandin; repaglinide-containing generics), increase insulin secretion to help control post-prandial blood glucose elevations.[5]

The 2018 American Diabetes Association (ADA) Standards of Medical Care in Diabetes recommendations include all currently available FDA-approved therapies for T2DM management.[6] The Standards recommend the initiation of metformin as first-line therapy at the time of T2DM diagnosis, except when contraindicated, in addition to lifestyle interventions. Insulin therapy should be considered, with or without additional agents, in newly diagnosed patients who are highly symptomatic and/or who have elevated blood glucose levels (≥ 300 mg/dL) or HbA1c (≥ 10%) from the onset. If a patient is not well controlled on a maximum recommended dose of a non-insulin agent after 3 months, a second oral agent (e.g., sulfonylurea (SU), thiazolidinedione (TZD), DPP-4 inhibitor, sodium-glucose cotransporter-2 (SGLT2) inhibitor), a glucagon-like peptide-1 (GLP-1) receptor agonist, or basal insulin should be added. Meglitinides may be considered, instead of sulfonylureas, in patients with sulfa allergies or irregular meal schedules or who develop late postprandial hypoglycemia on a sulfonylurea.

The ADA recommends maintaining a goal HbA1c < 7% for most nonpregnant adults and as low as 6.5% for select well managed patients with few adverse effects.[7] However, for patients with a history of severe hypoglycemia, shortened life expectancy, and other comorbid disease states, less stringent goals (HbA1c < 8%) may be appropriate. The ADA also recommends a target HbA1c < 7.5% for all pediatric patients.

In 2018, the American Academy of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) released updated clinical practice guidelines for developing a diabetes mellitus comprehensive care plan and management algorithm.[8] These guidelines have similar recommendations for diagnosing diabetes mellitus as the 2018 ADA guidelines. AACE/ACE continues to recommend a goal HbA1c ≤ 6.5% for most adults. Lifestyle modification, including medically assisted weight loss, underlies all treatments. AACE/ACE recommends that the choice of therapy must be based

on the individual patient factors such as other medications, cost, ease of use, risk factors, and patient's initial HbA1c level. AACE suggests patients with an HbA1c < 7.5% start with monotherapy; whereas patients with an HbA1c of 7.5% to 9% should begin with dual therapy. Patients with an HbA1c > 9% and no symptoms may start either dual or triple antihyperglycemic therapy; while patients with an HbA1c > 9% with symptoms should begin insulin therapy with or without other agents. The HbA1c should be reassessed every 3 months and failure to improve may warrant additional complementary therapy for optimal glycemic control. The guidelines provide prescribers a hierarchical order of the usage of drugs where metformin is the preferred treatment of choice for monotherapy and first-line agent for dual and triple therapy. For patients with HbA1c < 7.5% at onset, monotherapy with metformin is preferred; alternative as initial therapy include GLP-1 receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors, and thiazolidinediones. Monotherapy with an alpha-glucosidase inhibitor, a sulfonylurea, or a meglitinide may be appropriate in select patients.

In 2018, the ACP developed a statement to guide clinicians in selecting targets for pharmacologic treatment of T2DM, including recommending a goal HbA1c level between 7% and 8% in most patients.[9] In addition, they state that clinicians should consider deintensifying pharmacologic therapy in patients who achieve HbA1c levels < 6.5%, treat patients to minimize symptoms related to hyperglycemia, and avoid targeting an HbA1c level in patients with a life expectancy < 10 years due to advanced age because the harms outweigh the benefits in this population.

PHARMACOLOGY[10,11,12]

The meglitinides are non-sulfonylurea hypoglycemic agents that lower blood glucose levels by stimulating the release of insulin from the pancreas. Action of these agents is dependent on actively functioning beta cells in the pancreatic islets.

The meglitinides bind to a non-sulfonylurea receptor 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 hypoglycemic agent used in a fixed-dose combination with repaglinide. Metformin 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 (%)	Tmax (hr)	Half-life (hr)	Metabolism	Excretion (%)
metformin[13]	50-60	--	6.2-17.6	None	urine: > 90
nateglinide (Starlix)[14,15]	73	≤1	1.5	Hepatic (2C9 and 3A4); less potent metabolites	urine: 83 feces: 10
repaglinide (Prandin)[16]	56	≤1	1	Hepatic (2C8 and 3A4); 3 metabolites which do not contribute to glucose lowering effect	urine: 8 feces: 90

Fixed-dose combination repaglinide/metformin tablets are bioequivalent to the individual drugs administered together.

CONTRAINDICATIONS/WARNINGS[17,18,19]

Nateglinide (Starlix) and repaglinide (Prandin) are contraindicated in patients with type 1 diabetes, diabetic ketoacidosis, or a known hypersensitivity to the drug or its inactive ingredients. Repaglinide (Prandin) is contraindicated in patients also taking gemfibrozil.

Any product containing metformin is contraindicated in patients with any of the following: renal disease or renal dysfunction (estimated glomerular filtration (eGFR) rate < 30 mL/min/1.73 m^2), 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 contains a boxed warning related to an increased risk of lactic acidosis, especially in patients with renal or hepatic impairment, excessive alcohol intake, concomitant use of certain drugs, age > 65 years, radiological studies with contrast, volume depletion, or hypoxia. Post-marketing cases have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. 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 (Prandin, repaglinide-containing generics) should not be used with NPH insulin due to serious cardiovascular events observed in clinical studies in patients treated with both repaglinide and NPH insulin. During times of stress, such as fever, infection or surgery, nateglinide and repaglinide therapy may need to be discontinued and insulin started.

DRUG INTERACTIONS[20,21,22]

Close monitoring of blood glucose is recommended when adding or discontinuing drugs that can induce hyperglycemia.

Nateglinide (Starlix) and repaglinide (Prandin, repaglinide-containing generics) are highly protein bound (98%). When other highly protein-bound drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), salicylates, sulfonamides, coumarins, probenecid, monoamine oxidase inhibitors 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.

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, particularly if both enzymes are inhibited at the same time. Known inhibitors of CYP3A4 include ketoconazole, itraconazole, and erythromycin. Drugs that inhibit CYP2C8 include gemfibrozil, trimethoprim, and montelukast; coadministration of repaglinide and gemfibrozil is contraindicated.

Postmarketing events of serious hypoglycemia have been reported in patients taking both repaglinide and gemfibrozil. Repaglinide exposure is increased more than 20-fold in patients taking both gemfibrozil and itraconazole. CYP3A4 and CYP2C8 inducers include rifampin, carbamazepine, and barbiturates.

Repaglinide appears to be a substrate for active hepatic uptake transporter (organic anion transporting protein OATP1B1). Drugs that inhibit OATP1B1, like cyclosporine, may also have the potential to increase plasma concentrations of repaglinide.

Also, clopidogrel increases repaglinide exposure by 3.9- to 5.1-fold, therefore concomitant use of repaglinide and clopidogrel should be avoided if possible. If such avoidance of use with clopidogrel is not possible, then repaglinide should be initiated at 0.5mg before a meal and should not exceed 4mg daily; increase glucose monitoring may be needed as well.

Simvastatin, clarithromycin, levonorgestrel, and ethinyl estradiol have also been demonstrated to elevate repaglinide levels in healthy volunteers.

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

Concurrent use of drugs (e.g., ranolazine, vandetanib, dolutegravir, cimetidine) that interfere with renal tubular transport increase exposure to metformin and increase the risk of lactic acidosis. As such, combination repaglinide/metformin should be used cautiously with these agents.

ADVERSE EFFECTS[23,24,25]

Drug	URI	Diarrhea	Back Pain	Hypoglycemia	Dizziness	Headache
nateglinide (Starlix) n=1,441	10.5 (8.1)	3.2 (3.1)	4 (3.7)	2.4 (0.4)	3.6 (2.2)	nr
repaglinide (Prandin) n=352	16 (8)	5 (2)	5 (4)	31 (7)	nr	11 (10)
repaglinide/ metformin	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 or all inclusive. 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 reflect coadministration of repaglinide and metformin and were measured against monotherapy of metformin and repaglinide (Prandin). In clinical trials comparing repaglinide to sulfonylureas, the incidence of total serious cardiovascular adverse events, including ischemia, was higher for repaglinide (4%) than for sulfonylurea drugs (3%) in 1 year controlled trials. However, repaglinide was not associated with excess mortality rates when compared to observed mortality rates with other oral anti-diabetic drugs.[26]

SPECIAL POPULATIONS[27,28,29]

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. There are no adequate and well-controlled studies of nateglinide in pregnant women; therefore, it is unknown if these agents can cause fetal harm when administered during pregnancy.

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 [CrCl] 20 to 40 mL/min) should start repaglinide at 0.5 mg dose. Caution should be used in patients with CrCl < 20 mL/min and in patients on hemodialysis.

The use of combination repaglinide/metformin is contraindicated in patients with an estimated glomerular filtration rate (eGFR) of < 30 mL/minute/1.73 m^2 and it is not recommended at eGFR between 30 to 45 mL/minute/1.73 m^2 due to the metformin component. Assessment of eGFR should be done before the initiation and periodically after starting repaglinide/metformin. If it is assessed that the eGFR has fallen below 45 mL/minute/1.73 m^2 a risk vs. benefit analysis may be used. However repaglinide/metformin should be discontinued if eGFR is less than below 30 mL/minute/1.73 m^2.

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.

Geriatrics

Repaglinide/metformin should be use cautiously in elderly patients, typically initiating therapy at a dose at the low end of the dosage range. Assess renal function more frequently than younger patients.

Ethnic Groups

A randomized, controlled, double-blind, double-dummy trial enrolled 230 Chinese patients with T2DM.[30] Patients were dosed 3 times a day with either repaglinide (Prandin) 1 mg or nateglinide (i.e., Starlix) 90 mg. After 12 weeks, there was no significant difference between the repaglinide and nateglinide groups regarding reduction of fasting blood glucose or HbA1c (p>0.05 for each).

DOSAGES[31,32,33]

Drug	Parameters	Dosage	Availability
nateglinide (Starlix)	Initial therapy for patients near HbA1c goals (alone or in combination with metformin, pioglitazone, or rosiglitazone)	60 mg taken 1–30 minutes before each meal (3 times daily)	60 mg, 120 mg tablets
	Most patients (alone or in combination with metformin, pioglitazone, or rosiglitazone)	120 mg taken 1–30 minutes before each meal (3 times daily)	
repaglinide (Prandin)	Initial therapy or HbA1c < 8%	0.5 mg taken 0–30 minutes prior to each meal (2, 3, or 4 times daily)	0.5 mg, 1 mg, 2 mg tablets
	Previously treated with glucose-lowering drugs and HbA1c ≥ 8%	1 or 2 mg (and up to 4 mg) taken 0–30 minutes prior to each meal (2, 3, or 4 times daily); maximum daily dose is 16 mg	
repaglinide/metformin	Inadequately controlled with metformin monotherapy	Initiate dose at 1 mg/500 mg twice daily with meals taken 0–30 minutes prior to each meal (2, 3, or 4 times daily); 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 taken 0–30 minutes prior to each meal (2, 3, or 4 times daily)	
	Current concomitant use of metformin and repaglinide	Initiate dose of repaglinide and metformin similar to, but not exceeding, current doses; taken 0–30 minutes prior to each meal (2, 3, or 4 times daily)	

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.

Repaglinide/metformin can be administered 2 to 3 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% 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 U.S., 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 metformin (Glucophage®)

In a randomized, double-blind trial, patients with T2DM and HbA1c levels between 6.8% and 11% were given nateglinide 120 mg before meals (n=179), metformin 500 mg 3 times daily (n=178), combination therapy (n=172), or placebo (n=172) for 24 weeks.[34] HbA1c (nateglinide -0.5%, metformin -0.8%) and fasting plasma glucose (FPG) (nateglinide -0.7 mmol/L, metformin -1.6 mmol/L; p≤0.0001) were significantly lower in the treatment groups but increased in the placebo group (+0.5% for HbA1c and +0.4 mmol/L for FPG; both p<0.0001). Combination therapy provided an additive response compared to monotherapy (HbA1c -1.4%, FPG -2.4 mmol/L; p<0.01). The reduction in mealtime glucose was greater with nateglinide monotherapy and combination therapy compared with metformin monotherapy or placebo (adjusted area under the curve [AUC] 0 to 130 min -2.1, -2.5, -1.1, and -0.6 mmol/l·h; p≤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 patients with T2DM stabilized on high-dose metformin.[35] Metformin-treated patients with HbA1c between 6.8% and 11% were randomized to add nateglinide 60 mg, 120 mg, or placebo before 3 meals daily to metformin 1,000 mg twice daily for 24 weeks. HbA1c was significantly reduced with nateglinide 60 mg and 120 mg plus metformin compared with metformin control (-0.36%, p=0.003; -0.59%, p<0.001 respectively). Greater benefits occurred if patients had elevated HbA1c at baseline (-1.38% with nateglinide 120 mg in patients with HbA1c > 9.5%). A modest reduction in FPG was observed. Events suggestive of hypoglycemia were confirmed in 1.1% of cases. Most symptoms suggestive of hypoglycemia occurred in patients with lower HbA1c levels (< 8%) 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.

repaglinide (Prandin) and nateglinide (Starlix)

The efficacy and safety of repaglinide monotherapy and nateglinide monotherapy in patients with T2DM who were previously treated with diet and exercise were compared in a randomized, parallel-group, open-label, multicenter trial.[36] 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 HbA1c 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 HbA1c (-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 0 patients on 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 T2DM.[37] Patients had an HbA1c between 7% and 12% and had been previously treated with metformin or a sulfonylurea. After 4 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 HbA1c and the change in HbA1c from baseline. Secondary endpoints included FPG levels. Final HbA1c was lower for patients treated with repaglinide/metformin (7.1% versus 7.5%, respectively). Patients who were treated with repaglinide/metformin also had a significantly greater reduction in HbA1c 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 2 treatment groups were comparable.

repaglinide (Prandin) and metformin (Glucophage®)

In a multicenter double-blind trial, 83 patients with T2DM and inadequate glycemic control (HbA1c > 7.1%) on metformin were randomized to receive add-on repaglinide (n=27), repaglinide monotherapy (n=29), or to continue on metformin monotherapy (n=27).[38] The repaglinide dose was titrated for 4 to 8 weeks, followed by a 3-month dose maintenance period. In subjects receiving combination therapy, there was a significant reduction in both HbA1c (8.3% to 6.9%; p=0.0016) and FPG (by 2.2 mmol/L; p=0.0003). There were no significant changes observed in HbA1c 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 kg, respectively).

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.[39] 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 11 studies comparing meglitinides to placebo, both repaglinide (Prandin) and nateglinide (Starlix) resulted in reductions in

HbA1c (0.1% to 2.1% reduction in HbA1c for repaglinide; 0.2 to 0.6% for nateglinide). Only 2 trials compared repaglinide to nateglinide (342 total participants), with greater reduction in HbA1c 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. Current guidelines do not recommend meglitinides as a key component of an oral diabetes treatment regimen but state that a meglitinide may be used in select patients in place of a sulfonylurea. While this class should be used with caution, the meglitinides have been shown to control postprandial hyperglycemia in patients with T2DM and to lower HbA1c. Both repaglinide (Prandin) and nateglinide (Starlix) have similar indications and adverse effects, and direct comparative data of good quality are not available.

Repaglinide/metformin is available, generically, for patients who require multiple agents for treatment of T2DM.

REFERENCES

1 Starlix [package insert]. East Hanover, NJ; Novartis; March 2017.
2 Prandin [package insert]. Princeton, NJ; Novo Nordisk; February 2017.
3 Prandimet [package insert]. Princeton, NJ; Novo Nordisk; December 2017.
4 National Institute of Diabetes and Digestive and Kidney Diseases. National Diabetes Statistics Report 2017 fact sheet. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, 2017. https://www.niddk.nih.gov/health-information/health-statistics. Accessed January 10, 2018.
5 Available at: http://www.clinicalpharmacology-ip.com. Accessed January 23, 2018.
6 American Diabetes Association. Position Statement. Standards in medical care in diabetes – 2018. Diabetes Care. 2018; 41(Suppl 1):S1-159. DOI: 10.2337/dc18-SINT01 S009 Available at: https://professional.diabetes.org/content-page/standards-medical-care-diabetes. Accessed January 10. 2018.
7American Diabetes Association. Position Statement. Standards in medical care in diabetes – 2018. Diabetes Care. 2018; 41(Suppl 1):S1-159. DOI: 10.2337/dc18-SINT01 S009 Available at: https://professional.diabetes.org/content-page/standards-medical-care-diabetes. Accessed January 10. 2018.
8 Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm –2018. Executive Summary. Endocr Pract. 2017; 24 (1):94-120. Available at: https://www.aace.com/publications/guidelines. Accessed January 10, 2018.
9 Qaseen A, Wilt TJ, Kansagara D, et al. Hemoglobin A1c Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians. *Ann Intern Med.* 2018. Published on-line. **DOI:** 10.7326/M17-0939. Available at: https://www.acponline.org/clinical-information/guidelines. Accessed March 19, 2018.
10 Starlix [package insert]. East Hanover, NJ; Novartis; March 2017.
11 Prandin [package insert]. Princeton, NJ; Novo Nordisk; February 2017.
12 Prandimet [package insert]. Princeton, NJ; Novo Nordisk; December 2017.
13 Prandimet [package insert]. Princeton, NJ; Novo Nordisk; December 2017.
14 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.
15 Starlix [package insert]. East Hanover, NJ; Novartis; March 2017.
16 Prandin [package insert]. Princeton, NJ; Novo Nordisk; February 2017.
17 Starlix [package insert]. East Hanover, NJ; Novartis; March 2017.
18 Prandin [package insert]. Princeton, NJ; Novo Nordisk; February 2017.
19 Prandimet [package insert]. Princeton, NJ; Novo Nordisk; December 2017.
20 Starlix [package insert]. East Hanover, NJ; Novartis; March 2017.
21 Prandin [package insert]. Princeton, NJ; Novo Nordisk; February 2017.
22 Prandimet [package insert]. Princeton, NJ; Novo Nordisk; December 2017.
23 Starlix [package insert]. East Hanover, NJ; Novartis; March 2017.
24 Prandin [package insert]. Princeton, NJ; Novo Nordisk; February 2017.
25 Prandimet [package insert]. Princeton, NJ; Novo Nordisk; December 2017.
26 Prandin [package insert]. Princeton, NJ; Novo Nordisk; February 2017.
27 Starlix [package insert]. East Hanover, NJ; Novartis; March 2017.
28 Prandin [package insert]. Princeton, NJ; Novo Nordisk; February 2017.
29 Prandimet [package insert]. Princeton, NJ; Novo Nordisk; December 2017.
30 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.

31 Starlix [package insert]. East Hanover, NJ; Novartis; March 2017.
32 Prandin [package insert]. Princeton, NJ; Novo Nordisk; February 2017.
33 Prandimet [package insert]. Princeton, NJ; Novo Nordisk; December 2017.
34 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.
35 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.
36 Rosenstock J, Hassman DR, Maddor RD, et al. Repaglinide versus nateglinide monotherapy: a randomized, multicenter study. Diabetes Care. 2004; 27(6):1265-1270.
37 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.
38 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.
39 Black C, Donnelly P, McIntyre L, et al. Meglitinide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007; (2):CD004654.