HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PrandiMet safely and effectively. See full prescribing information for PrandiMet.

PrandiMet® (repaglinide and metformin HCl) Tablets
Initial U.S. Approval: 2008

WARNING: LACTIC ACIDOSIS
See full prescribing information for complete boxed warning

- **Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. (5.1)**
- **Risk factors include renal impairment, concomitant use of certain drugs, age > 65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5.1)**
- **If lactic acidosis is suspected, discontinue PrandiMet and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended . (5.1)**

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·····RECENT MAJOR CHANGES·····

Boxed Warning	4/2017
Dosing and Administration (2.2)	4/2017
Contraindications (4)	4/2017
Warnings and Precautions (5.1)	4/2017

·····INDICATIONS AND USAGE·····

- PrandiMet is a meglitinide and biguanide combination product indicated as an 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 HCl or who have inadequate glycemic control on a meglitinide alone or metformin HCl alone. (1)

Important Limitations of Use:

- Do not use to treat type 1 diabetes or diabetic ketoacidosis. (1)

·····DOSAGE AND ADMINISTRATION·····

- The dosage of PrandiMet should be individualized, starting with 1 mg/500 mg twice daily unless the patient is already taking higher co-administered doses of repaglinide and metformin HCl. (2.1)
- Do not exceed 10 mg repaglinide/2500 mg metformin HCl daily or 4 mg repaglinide/1000 mg metformin HCl per meal. (2.1)
- Give in divided doses within 15 minutes prior to meals. (2.1)
- Patients who skip a meal should skip the PrandiMet dose for that meal. (2.1)
- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR) (2.2)
  - o Do not use in patients with eGFR below 30 mL/minute/1.73 m2
  - o Initiation is not recommended in patients with eGFR between 30 – 45 mL/minute/1.73 m2
  - o Assess risk/benefit of continuing if eGFR falls below 45 mL/minute/1.73 m2
  - o Discontinue if eGFR falls below 30 mL/minute/1.73 m2
- PrandiMet may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures (2.3)

·····DOSAGE FORMS AND STRENGTHS·····

Tablets:

- 1 mg repaglinide/500 mg metformin HCl (3)
- 2 mg repaglinide/500 mg metformin HCl (3)

·····CONTRAINDICATIONS·····

Do not use in patients:

- with severe renal impairment (eGFR below 30 mL/min/1.73 m2). (4, 5.1)
- with metabolic acidosis, including diabetic ketoacidosis. (4, 5.1)
- receiving gemfibrozil. (4, 5.3, 7.4, 12.3)

·····WARNINGS AND PRECAUTIONS·····

- Lactic acidosis: See boxed warning. (4, 5.1)
- PrandiMet should not be used in combination with NPH insulin. (5.2)
- Gemfibrozil substantially increases repaglinide exposure. Coadministration of gemfibrozil and PrandiMet is not recommended. (4, 5.3, 7.2, 12.3)
- The repaglinide component can cause hypoglycemia. Initiate PrandiMet at the lowest available dose in patients naive to meglitinide therapy. (5.4)
- Vitamin B_{12} deficiency: Metformin can lower vitamin B_{12} levels. Monitor hematological parameters annually. (5.5)
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with PrandiMet or any other oral anti-diabetic drug. (5.8)

·····ADVERSE REACTIONS·····

- Hypoglycemia and headache were the most common adverse reactions (≥10%) reported among patients treated with repaglinide in combination with metformin HCl, occurring more frequently than among patients treated with repaglinide alone or metformin HCl alone. (6.2)
- Gastrointestinal reactions (e.g., diarrhea, nausea and vomiting) are the most common adverse reactions with metformin HCl treatment and are more frequent at higher metformin HCl doses. (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-800-727-6500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

·····DRUG INTERACTIONS·····

- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7.1)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use. (7.2)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn
  patients against excessive alcohol intake. (7.3)
- Repaglinide is partly metabolized by CYP2C8 and CYP3A4. Use caution in patients taking inhibitors and/or inducers of CYP2C8 and CYP3A4. (7.4)

…… USE IN SPECIFIC POPULATIONS……

- Geriatric Use: Assess renal function more frequently. (8.5)
- Hepatic Impairment: Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 4/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (> 5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL *[see Warnings and Precautions (5.1)]*.

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anyhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information *[see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)]*.

If metformin-associated lactic acidosis is suspected, immediately discontinue PrandiMet and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

PrandiMet is indicated as an 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 HCl or who have inadequate glycemic control on a meglitinide alone or metformin HCl alone.

Important Limitations of Use:

PrandiMet should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The dosage of PrandiMet should be individualized on the basis of the patient's current regimen, effectiveness and tolerability. PrandiMet can be administered 2 to 3 times a day up to a maximum daily dose of 10 mg repaglinide/2500 mg metformin HCl. No more than 4 mg repaglinide/1000 mg metformin HCl should be taken per meal. Initiation and maintenance of combination therapy with PrandiMet should be individualized to the patient, and at the discretion of the health care provider. Blood glucose monitoring should be performed to determine the therapeutic response to PrandiMet.

PrandiMet doses should usually be taken within 15 minutes prior to the meal but the timing can vary from immediately preceding the meal up to 30 minutes before the meal. Patients who skip a meal should be instructed to skip the PrandiMet dose for that meal.

Patients Inadequately Controlled with Metformin HCl Monotherapy

If therapy with a combination tablet containing repaglinide and metformin HCl is considered appropriate for a patient with type 2 diabetes mellitus inadequately controlled with metformin HCl alone, the recommended starting dose of PrandiMet is 1 mg repaglinide/500 mg metformin HCl administered twice daily with meals, with gradual dose escalation (based on glycemic response) to reduce the risk of hypoglycemia with repaglinide.

Patients Inadequately Controlled with Meglitinide Monotherapy

If therapy with a combination tablet containing repaglinide and metformin HCl is considered appropriate for a patient with type 2 diabetes mellitus inadequately controlled with repaglinide alone, the recommended starting dose of the metformin HCl component of PrandiMet should be 500 mg metformin HCl twice a day, with gradual dose escalation (based on glycemic response) to reduce gastrointestinal side effects associated with metformin HCl.

Patients Currently Using Repaglinide and Metformin HCl Concomitantly

For patients switching from repaglinide co-administered with metformin HCl, PrandiMet can be initiated at the dose of repaglinide and metformin HCl similar to (but not exceeding) the patient's current doses, then may be titrated to the maximum daily dose as necessary to achieve targeted glycemic control.

No studies have been performed examining the safety and efficacy of PrandiMet in patients previously treated with other oral antihyperglycemic agents and switched to PrandiMet. Any change in therapy should be undertaken with care and with appropriate monitoring as changes in glycemic control can occur.

2.2 Recommendations for Use in Renal Impairment

Assess renal function with an estimated glomerular filtration rate (eGFR) prior to initiation of PrandiMet and periodically thereafter.
PrandiMet is contraindicated in patients with an eGFR below 30 mL/min/1.73 m2.
Initiation of PrandiMet in patients with an eGFR between 30 – 45 mL/min/1.73 m2 is not recommended.
In patients taking PrandiMet whose eGFR later falls below 45 mL/min/1.73 m2, assess the benefit-risk of continuing therapy.
Discontinue PrandiMet if the patient's eGFR later falls below 30 mL/min/1.73 m2 *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

2.3 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue PrandiMet at the time or, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart PrandiMet if renal function is stable *[See Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

- 1 mg repaglinide /500mg metformin HCl tablets are yellow, biconvex, debossed with Novo Nordisk (Apis) bull symbol on one side, and strength indicated on the other side
- 2 mg repaglinide /500mg metformin HCl tablets are pink, biconvex, debossed with Novo Nordisk (Apis) bull symbol on one side, and strength indicated on the other side

4 CONTRAINDICATIONS

PrandiMet is contraindicated in:

- Severe renal impairment (GFR below 30 mL/min. 1.73 m^2) *[see Warnings and Precautions (5.1)]*.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin *[see Warnings and Precautions (5.1)]*.
- Patients receiving gemfibrozil *[see Warnings and Precautions (5.7), Drug Interactions (7.2), Clinical Pharmacology (12.3)]*.
- Patients with known hypersensitivity to repaglinide, metformin HCl or any inactive ingredients in PrandiMet.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

Metformin hydrochloride

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate:pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of PrandiMet. In PrandiMet treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue PrandiMet and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]:*

- Before initiating PrandiMet, obtain an estimated glomerular filtration rate (eGFR).
- PrandiMet is contraindicated in patients with an eGFR less than 30 mL/minute/1.73 m2*[see Contraindiations (4)]* .
- Initiation of PrandiMet is not recommended in patients with eGFR between 30 – 45 mL/minute/1.73 m2.
- Obtain an eGFR at least annually in all patients taking PrandiMet. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- In patients taking PrandiMet whose eGFR later falls below 45 mL/min/1.73 m2, assess the benefit and risk of continuing therapy.

Drug Interactions: The concomitant use of PrandiMet with specific drugs may increase the risk of metformin- associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation *[see Drug Interactions (7)]*. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients [*see Use in Specific Populations (8.5)]*.

Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop PrandiMet at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart PrandiMet if renal function is stable.

Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. PrandiMet should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue PrandiMet.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving PrandiMet.

Hepatic Impairment: Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of PrandiMet in patients with clinical or laboratory evidence of hepatic disease.

5.2 Combination with NPH-insulin

Repaglinide

Repaglinide is not indicated for use in combination with NPH-insulin.

Across seven controlled clinical trials, there were six serious adverse events (1.4%) of myocardial ischemia with repaglinide in combination with NPH-insulin compared to one event (0.3%) in patients using insulin alone *[see Adverse Reactions (6.2)]*.

5.3 Drug Interactions

Repaglinide is partly metabolized by CYP2C8 and CYP3A4 and appears to be a substrate for active hepatic uptake transporter (organic anion transporting protein OATP1B1). Drugs that inhibit CYP2C8, CYP3A4, or OATP1B1 (e.g., cyclosporine) may

increase plasma concentrations of repaglinide. Dose reduction of repaglinide may be needed *[see Drug Interactions (7.4) and Clinical Pharmacology (12.3)]*.

Gemfibrozil significantly increased repaglinide exposure. Therefore, patients should not take PrandiMet with gemfibrozil *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

5.4 Hypoglycemia

Most blood glucose-lowering drugs, including repaglinide, can cause hypoglycemia. Patients who have not previously been treated with a meglitinide should be started on the lowest available repaglinide component of PrandiMet to reduce the risk of hypoglycemia. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemia. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking β-adrenergic blocking drugs *[see Adverse Reactions (6.1)]*.

5.5 Vitamin B_{12} Levels

In controlled clinical trials of metformin HCl of 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. This finding, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin HCl or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on PrandiMet and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at 2- to 3-year intervals may be useful.

5.6 Loss of Control of Blood Glucose

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold PrandiMet and temporarily administer insulin. PrandiMet may be reinstituted after the acute episode is resolved.

5.7 Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes

A patient with type 2 diabetes previously well-controlled on PrandiMet who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, PrandiMet must be stopped immediately and other appropriate corrective measures initiated.

5.8 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with PrandiMet or any other oral anti-diabetic drug.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling.

- Lactic acidosis *[see Warnings and Precautions (5.1)]*
- Hypoglycemia *[see Warnings and Precautions (5.4)]*
- Vitamin B_{12} levels*[see Warnings and Precautions (5.5)]*

6.1 Most Frequently Observed Adverse Reactions

Repaglinide

In clinical trials of repaglinide, hypoglycemia is the most common adverse reaction (> 5%) leading to withdrawal of patients treated with repaglinide.

Metformin HCl

Gastrointestinal reactions (e.g., diarrhea, nausea, vomiting) are the most common adverse reactions (> 5%) with metformin HCl treatment and are more frequent at higher metformin HCl doses.

6.3 Clinical Trial Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Patients with Inadequate Glycemic Control on Metformin HCl Monotherapy

Table 1 summarizes the most common adverse reactions occurring in a 6-month randomized study of repaglinide added to metformin HCl in patients with type 2 diabetes inadequately controlled on metformin HCl alone.

Table 1: Repaglinide added to metformin HCl in patients with type 2 diabetes inadequately controlled on metformin HCl alone. Adverse reaction reported (regardless of Investigator Assessment of Causality) in ≥10% of patients receiving combination therapy*

	Coadministered repaglinide and metformin HCl	Metformin HCl monotherapy	Repaglinide monotherapy
	N (%)	N (%)	N (%)
No. of Patients Exposed	27	27	28
Gastrointestinal System Disorder	9 (33)	13 (48)	10 (36)
Diarrhea	5 (19)	8 (30)	2 (7)
Nausea	4 (15)	2 (7)	1 (4)
Symptomatic Hypoglycemia **	9 (33)	0 (0)	3 (11)
Headache	6 (22)	4 (15)	3 (11)
Upper Respiratory Tract Infection	3 (11)	3 (11)	3 (11)

*Intent to treat population

** There were no cases of severe hypoglycemia (hypoglycemia requiring the assistance of another person)

Cardiovascular Events in repaglinide monotherapy trials

In one-year trials comparing repaglinide to sulfonylurea drugs, the incidence of angina was 1.8% for both treatments, with an incidence of chest pain of 1.8% for repaglinide and 1.0% for sulfonylureas. The incidence of other selected cardiovascular events (hypertension, abnormal electrocardiogram, myocardial infarction, arrhythmias, and palpitations) was ≤ 1% and not different between repaglinide and the comparator drugs.

The incidence of total serious cardiovascular adverse events, including ischemia, was higher for repaglinide (51/1228 or 4%) than for sulfonylurea drugs (13/498 or 3%) in controlled clinical trials. In 1-year controlled trials, repaglinide treatment was not associated with excess mortality when compared to the rates observed with other oral hypoglycemic agent therapies such as glyburide and glipizide.

Seven controlled clinical trials included repaglinide combination therapy with NPH-insulin (n=431), insulin formulations alone (n=388) or other combinations (sulfonylurea plus NPH-insulin or repaglinide plus metformin HCl) (n=120). There were six serious adverse events of myocardial ischemia in patients treated with repaglinide plus NPH-insulin (1.4%) from two studies, and one event in patients using insulin formulations alone from another study (0.3%) *[see Warnings and Precautions (5.6)]*.

6.4 Postmarketing Experience

The following additional adverse reactions have been identified during postapproval use. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or a causal relationship to drug exposure.

Repaglinide

Alopecia, hemolytic anemia, pancreatitis, Stevens-Johnson Syndrome, and severe hepatic dysfunction including jaundice and hepatitis.

Metformin HCL

Cholestatic, hepatocellular, and mixed hepatocellular liver injury

7 DRUG INTERACTIONS

7.1 Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with PrandiMet may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

7.2 Drugs that reduce metformin clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Clinical Pharmacology (12.3)]*. Consider the benefits and risks of concomitant use.

7.3 Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving PrandiMet.

7.4 CYP2C8 and CYP3A4 Inhibitors/Inducers

Repaglinide is metabolized by CYP2C8 and to a lesser extent by CYP3A4. Drugs that inhibit 2C8 (gemfibrozil, trimethoprim, deferasirox), inhibit 3A4 (itraconazole, ketaconazole), or induce CYP2C8/3A4 (rifampin) may alter the pharmacokinetics and pharmacodynamics of repaglinide. In vivo data from a study that evaluated the co-administration of gemfibrozil and repaglinide in healthy subjects showed a significant increase in repaglinide blood levels. Administration of PrandiMet and gemfibrozil to the same patient is not recommended *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

Repaglinide exposures are increased more than 20-fold in patients taking both gemfibrozil and itraconazole *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women with PrandiMet or its individual components. Because animal reproduction studies are not always predictive of human response, PrandiMet like other antidiabetic medications, should be used during pregnancy only if clearly needed.

No animal studies have been conducted with the combined products in PrandiMet. The following data are based on findings in studies performed with repaglinide or metformin individually.

Repaglinide

Repaglinide was not teratogenic in rats at doses 40 times, and rabbits approximately 0.8 times the clinical exposure (on a mg/m^2 basis) throughout pregnancy. Offspring of rat dams exposed to repaglinide at 15 times clinical exposure on a mg/m^2 basis during days 17 to 22 of gestation and during lactation developed nonteratogenic skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. This effect was not seen at doses up to 2.5 times clinical exposure (on a mg/m^2 basis) on days 1 to 22 of pregnancy or at higher doses given during days 1 to 16 of pregnancy. Relevant human exposure has not occurred to date and therefore the safety of repaglinide administration throughout pregnancy or lactation cannot be established.

Metformin HCl

Metformin HCl alone was not teratogenic in rats or rabbits at doses up to 600 mg/kg/day. This represents an exposure of approximately two and six times the near-maximal efficacious human daily dose of 2000 mg of the metformin HCl component of PrandiMet based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

8.3 Nursing Mothers

No studies in lactating animals have been conducted with the PrandiMet fixed dose combination. In studies performed with individual components, both repaglinide and metformin are excreted into milk of lactating rats.

Repaglinide

In rat reproduction studies, measurable levels of repaglinide were detected in the breast milk of the dams and lowered blood glucose levels were observed in the pups. Cross fostering studies indicated that skeletal changes could be induced in control pups nursed by treated dams, although this occurred to a lesser degree than those pups treated in utero.

Metformin HCl

Studies in lactating rats with metformin HCl show that it is excreted into milk and reaches levels comparable to those in plasma.

It is not known whether repaglinide or metformin are excreted in human milk. PrandiMet is not recommended in nursing mothers because it may potentially cause hypoglycemia in nursing infants.

8.4 Pediatric Use

Safety and effectiveness of PrandiMet in pediatric patients have not been established. PrandiMet is not recommended for use in children.

8.5 Geriatric Use

Healthy volunteers treated with repaglinide 2 mg before each of 3 meals, showed no significant differences in repaglinide pharmacokinetics between the group of patients <65 years of age and those ≥65 years of age.

In patients with advanced age, PrandiMet should be carefully titrated to establish the minimum dose for adequate glycemic effect. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients. *[see Warnings and Precautions (5.1), Contraindications (4), Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. PrandiMet is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m2. *[See Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*

8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. PrandiMet is not recommended in patients with hepatic impairment. *[See Warnings and Precautions (5.1)]*

10 OVERDOSAGE

PrandiMet

No data are available with regard to overdose of PrandiMet. Findings related to the individual active substances are listed below.

Repaglinide

In a clinical trial, dizziness, headache, and diarrhea were reported in subjects receiving increasing doses of repaglinide up to 80 mg a day for 14 days. Hypoglycemia did not occur when meals were given with these high doses.

Hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery. There is no evidence that repaglinide is dialyzable using hemodialysis. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL.

Metformin HCl

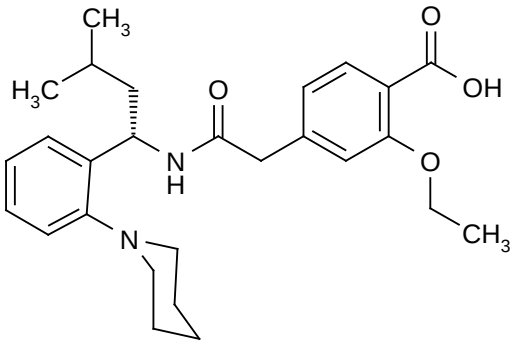
Overdose of metformin HCl has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin HCl has been established. Lactic acidosis has been reported in approximately 32% of metformin HCl overdose cases *[see Warnings and Precautions (5.1)]*. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin HCl overdosage is suspected.

11 DESCRIPTION

PrandiMet (repaglinide and metformin HCl) tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: repaglinide and metformin HCl. The concomitant use of repaglinide and metformin HCl has been previously approved based on clinical trials in patients with type 2 diabetes inadequately controlled on exercise, diet, and metformin HCl alone.

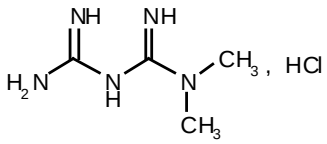
Repaglinide, S(+)2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid, is chemically unrelated to the oral sulfonylurea insulin secretagogues. Repaglinide is a white to off-white powder with molecular formula $C_{27}\ H_{36}\ N_2\ O_4$ and a molecular weight of 452.6 with the structural formula as shown below. Repaglinide is freely soluble in methanol and ethanol. The pKa of repaglinide in acid is 3.9, and the pKa in amine is 6.0.

Structural formula of Repaglinide



Metformin HCl (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin HCl is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Metformin HCl is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin HCl is 12.4. The pH of a 1% aqueous solution of metformin HCl is 6.68. The structural formula of metformin HCl is:

Structural formula of Metformin HCl



PrandiMet is available as a tablet for oral administration containing 1 mg repaglinide with 500 mg metformin HCl (1 mg/500 mg) or 2 mg repaglinide with 500 mg metformin HCl (2 mg/500 mg) formulated with the following inactive ingredients: poloxamer 188**,** microcrystalline cellulose, polacrillin potassium, magnesium stearate, hypromellose 3cp or 6cp, povidone, meglumine, sorbitol, talc, titanium dioxide, red or yellow iron oxide, and polyethylene glycol. Propylene glycol is present in the 2 mg/500 mg PrandiMet tablets.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PrandiMet

PrandiMet combines two anti-hyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes.

Repaglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta (ß) cells in the pancreatic islets.

Repaglinide closes ATP-dependent potassium channels in the ß-cell membrane by binding at characterizable sites. This potassium channel blockade depolarizes the ß-cell, which leads to an 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 an anti-hyperglycemic agent, which improves glucose tolerance in patients with type 2 diabetes by lowering both the basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

12.3 Pharmacokinetics

PrandiMet

The results of a bioequivalence study in healthy subjects (Table 2) demonstrated that PrandiMet (repaglinide/metformin HCl) 1 mg/500 mg and 2 mg/500 mg combination tablets are bioequivalent to co-administration of corresponding doses of repaglinide and metformin HCl as individual tablets. Repaglinide dose proportionality was demonstrated for PrandiMet (2 mg/500 mg) and PrandiMet (1 mg/500 mg).

Table 2. Mean (SD) Pharmacokinetic Parameters for Repaglinide and Metformin

		Pharmacokinetic Parameter	
Treatment	**N**	**AUC (ng·h/mL)**	**C_{max} (ng/mL)**
Repaglinide			
A	55	34.5 (13.3)	26.0 (13.7)
B	55	35.0 (13.2)	23.7 (12.5)
C	55	17.6 (6.6)	12.9 (6.9)
Metformin			
A	55	6041.9 (1494.6)	838.8 (210.2)
B	55	5871.6 (1352.6)	805.9 (160.3)
C	55	5948.9 (1442.0)	799.4 (174.6)

Treatment:
A = 2 mg/500 mg PrandiMet tablet
B = 2 mg repaglinide tablet + 500 mg metformin HCl tablet
C = 1 mg/500 mg PrandiMet tablet

Absorption and Bioavailability

Repaglinide: After single and multiple oral doses in healthy subjects or in patients with type 2 diabetes, peak plasma drug levels (C_{max}) occur within 1 hour (T_{max}). Repaglinide is eliminated from the blood stream with a half-life of approximately 1 hour. The mean absolute bioavailability is 56%. When repaglinide was given with food, the mean T_{max} was not changed, but the mean C_{max} and AUC (area under the time/plasma concentration curve) were decreased 20% and 12.4%, respectively.

Metformin HCl: The absolute bioavailability of a 500 mg metformin HCl tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin HCl tablets of 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower peak concentration (C_{max}), a 25% lower area under plasma concentration (AUC) and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin HCl with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Repaglinide: After intravenous (IV) dosing in healthy subjects, the volume of distribution at steady state (Vss) was 31 L, and the total body clearance (CL) was 38 L/h. Protein binding and binding to human serum albumin was greater than 98%.

Metformin HCl: The apparent volume of distribution (V/F) of metformin following single oral dose of 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin HCl, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally < 1 μg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 μg/mL, even at maximum doses.

Metabolism and Elimination

Repaglinide: Repaglinide is completely metabolized by oxidative biotransformation and direct conjugation with glucuronic acid after either an intravenous or oral dose. The major metabolites are an oxidized dicarboxylic acid (M2), the aromatic amine (M1), and the acyl glucuronide (M7). The cytochrome P-450 enzyme system, specifically 2C8 and 3A4, have been shown to be involved in the N-dealkylation of repaglinide to M2 and the further oxidation to M1. Metabolites do not contribute to the glucose-lowering effect of repaglinide. Within 96 hours after dosing with ^{14}C-repaglinide as a single, oral dose, approximately 90% of the radiolabel was recovered in the feces and approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound. The major metabolite (M2) accounted for 60% of the administered dose. Less than 2% of parent drug was recovered in feces. Repaglinide appears to be a substrate for active hepatic uptake transporter (organic anion transporting protein OATP1B1).

Metformin HCl: Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations

Renal Impairment

Repaglinide

Single-dose and steady-state pharmacokinetics of repaglinide were compared between patients with type 2 diabetes and normal renal function (CrCl > 80 mL/min), mild to moderate renal function impairment (CrCl = 40 – 80 mL/min), and severe renal function impairment (CrCl = 20 – 40 mL/min). Both AUC and C_{max} of repaglinide were similar in patients with normal and mild to moderately impaired renal function (mean values 56.7 ng/mL*hr vs 57.2 ng/mL*hr and 37.5 ng/mL vs 37.7 ng/mL, respectively). Patients with severely reduced renal function had elevated mean AUC and C_{max} values (98.0 ng/mL*hr and 50.7 ng/mL, respectively), but this study showed only a weak correlation between repaglinide levels and creatinine clearance.

Metformin HCl

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Hepatic Impairment

Repaglinide

A single-dose, open-label study was conducted in 12 healthy subjects and 12 patients with chronic liver disease (CLD) classified by Child-Pugh scale and caffeine clearance. Patients with moderate to severe impairment of liver function had higher and more prolonged serum concentrations of both total and unbound repaglinide than healthy subjects ($AUC_{healthy}$: 91.6 ng/mL*hr; $AUC_{CLD\ patients}$: 368.9 ng/mL*hr; $C_{max,\ healthy}$: 46.7 ng/mL; $C_{max,\ CLD\ patients}$: 105.4 ng/mL). AUC was statistically correlated with caffeine clearance. No difference in glucose profiles was observed across patient groups. Patients with impaired liver function may be exposed to higher concentrations of repaglinide and its associated metabolites than would patients with normal liver function receiving usual doses. Therefore, repaglinide should generally be avoided in patients with impaired liver function.

Metformin HCl

No pharmacokinetics studies with metformin HCl have been conducted in patients with hepatic impairment.

Geriatric Patients

Healthy volunteers treated with repaglinide 2 mg before each of 3 meals, showed no significant differences in repaglinide pharmacokinetics between the group of patients <65 years of age and those ≥65 years of age.

Limited data from controlled pharmacokinetic studies of metformin HCl in healthy elderly subjects suggest that total plasma clearance is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data,

it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function *[see Warnings and Precautions (5.2)]*.

Drug Interactions

Table 3: Effect of Other Drugs on AUC and C_{max} of Metformin

Study Drug*	Metformin AUC	Metformin C_{max}
Cimetidine	40% ↑	60% ↑
Furosemide	15% ↑	22% ↑
Nifedipine	9% ↑	20% ↑
Propranolol-metformin	10% ↓	6% ↓
Ibuprofen-metformin	5% ↑	7% ↑

Unless indicated all drug interactions were observed with single dose co-administration

*single and multiple dose co-administration

↑ indicates increase

↓ indicates decrease

Table 4: Effect of Other Drugs on AUC and C_{max} of Repaglinide

Study Drug	Dose Other Drug	Duration Other Drug	Repaglinide AUC	Repaglinide C_{max}
Clarithromycin*	250 mg BID	4 days	40% ↑	67% ↑
Cyclosporine	100 mg [5]	1 day	2.5 fold ↑	1.8 fold ↑
Deferasirox*	30 mg/kg QD [6]	4 days	2.3 fold ↑	62% ↑
Fenofibrate	200 mg QD	5 days	0%	18% ↑
Gemfibrozil*[1]	600 mg BID	3 days	8.1 fold ↑	2.4 fold ↑
Itraconazole*	100 mg BID	3 days	1.4 fold ↑	1.5 fold ↑
Gemfibrozil + **Itraconazole** Co-administration*[1]	Gem: 600 mg BID; Itra: 100 mg BID	3 days	19 fold ↑	2.8 fold ↑
Ketoconazole[2]	200 mg QD	4 days	15% ↑	16% ↑
Levonorgestrel/ethinyl Estradiol [3]	(0.15 mg/0.03 mg) Combination tablet QD	21 days	1.4% ↓	20% ↑
Nifedipine*[3]	10 mg TID	4 days	10% ↓	5% ↓
Rifampin*[4]	600 mg QD	6 - 7 days	32 – 80% ↓	17 - 79% ↓
Simvastatin[3]	20 mg QD	4 days	2% ↑	26% ↑
Trimethoprim*	160 mg BID	3 days	61% ↑	41% ↑

Unless indicated all drug interactions were observed with single dose of 0.25 mg repaglinide

[1] Coadministration of gemfibrozil with PrandiMet is not recommended *[see Warnings and Precautions (5.7) and Drug Interactions (7.2)]*

[2] Single dose of 2 mg repaglinide was administered

[3] 2 mg repaglinide was administered TID for 4 days

[4] Single dose of 4 mg repaglinide was administered

[5] Two doses, twelve hours apart, healthy volunteers

[6] Single dose of 0.5 mg repaglinide was administered

↑ indicates increase

↓ indicates decrease

* Indicates data are from published literature

Table 5: Effect of Metformin or Repaglinide on AUC and C_{max} of Other Drugs

Other Drugs	AUC	C_{max}
Furosemide [1]	12% ↓	31% ↓
Ethinyl Estradiol [2]	20% ↑	20% ↑
Fenofibrate	0%	18% ↑

[1] When administered with metformin

[2] Co-administration of a combination tablet (0.15 mg levonorgestrel/0.03 mg ethinyl estradiol) once daily for 21 days with 2 mg repaglinide administered TID (days 1-4) and a single dose on day 5.

↓ indicates decrease

↑ indicates increase

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

PrandiMet

No animal studies have been conducted with the combined products in PrandiMet to evaluate carcinogenesis, mutagenesis and impairment of fertility. The following data are based on findings in studies performed with the individual components.

Repaglinide

In a 104-week carcinogenicity study in rats at doses up to 120 mg/kg/day, the incidences of benign adenomas of the thyroid and liver were increased in male rats. The higher incidences of thyroid and liver tumors in male rats were not seen at lower dose of 30 mg/kg/day and 60 mg/kg/day respectively (which are over 15 and 30 times, respectively, clinical exposures on a mg/m^2 basis).

In a 104-week carcinogenicity study in mice at doses up to 500 mg/kg/day, no evidence of carcinogenicity was found in mice (which is approximately 125 times clinical exposure on a mg/m^2 basis).

Repaglinide was non-genotoxic in a battery of *in vivo* and *in vitro* studies: Bacterial mutagenesis (Ames test), *in vitro* forward cell mutation assay in V79 cells (HGPRT), *in vitro* chromosomal aberration assay in human lymphocytes, unscheduled and replicating DNA synthesis in rat liver, and *in vivo* mouse and rat micronucleus tests.

In a rat fertility study, repaglinide was administered to male and female rats at doses up to 300 and 80 mg/kg/day, respectively. No adverse effects on fertility were observed (which are over 40 times clinical exposure on a mg/m^2 basis).

Metformin HCl

In a 104-week carcinogenicity study in rats at doses up to 900 mg/kg/day, the incidences of benign stromal uterine polyps were increased in female rats at 900 mg/kg/day (which is approximately four times the maximal recommended human daily dose of 2000 mg of metformin HCl component of PrandiMet on a mg/m^2 basis).

In a 91-week carcinogenicity study in mice at doses up to 1500 mg/kg/day, no evidence of carcinogenicity was found in mice (which is approximately four times the maximal recommended human daily dose of 2000 mg of metformin HCl component of PrandiMet on a mg/m^2 basis).

There was no evidence of a mutagenic potential of metformin HCl alone in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

In a rat fertility study, metformin HCl was administered to male and female rats at doses up to 600 mg/kg/day. No adverse effects on fertility were observed (which is approximately three times the maximal recommended human daily dose of 2000 mg of metformin HCl component of PrandiMet on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Patients with Inadequate Glycemic Control on Metformin HCl Monotherapy

In a double-blind, clinical trial, 83 patients with type 2 diabetes and inadequate glycemic control on metformin HCl monotherapy were randomized to add-on repaglinide, repaglinide monotherapy, or continued treatment with metformin HCl monotherapy. The repaglinide dosage was titrated for 4 to 8 weeks, followed by a 3-month dose maintenance period. Repaglinide add-on to metformin HCl resulted in a statistically significant improvement in HbA_{1c} and fasting plasma glucose compared to the monotherapy arms (Table 6). In this study where metformin HCl dosage was kept constant, repaglinide add-on to metformin HCl resulted in a greater reduction in HbA_{1c} and fasting plasma glucose at a lower daily repaglinide dosage than in the repaglinide monotherapy group (dose sparing with respect to repaglinide). However, the repaglinide add-on to metformin HCl group had a higher incidence of hypoglycemia than the repaglinide monotherapy group *[see Adverse Reactions (6.2)]*. The 2 repaglinide treatment arms experienced weight gain, whereas the metformin HCl monotherapy arm had weight loss.

Table 6. Repaglinide as Add-on to Metformin HCl: Mean Changes from Baseline in Glycemic Parameters and Body Weight After 4 to 5 Months of Treatment[1]

	Repaglinide add-on to Metformin HCl	Repaglinide monotherapy	Metformin HCl monotherapy
N	27	28	27
Median Final Dose (mg/day)	6 (repaglinide) 1500 (metformin HCl)	12	1500
HbA_{1c} (%)			
Baseline	8.3	8.6	8.6
Change from baseline	-1.4*	-0.4	-0.3
Fasting plasma glucose (mg/dL)			
Baseline	184	174	194
Change from baseline	-39*	+9	-5
Weight (kg)			
Baseline	93	87	91
Change from baseline	2.4#	3.0	-0.9

1: based on intent-to-treat analysis

*: $p < 0.05$, for pairwise comparisons with repaglinide and metformin HCl monotherapy.

#: $p < 0.05$, for pairwise comparison with metformin HCl monotherapy.

16 HOW SUPPLIED/STORAGE AND HANDLING

PrandiMet tablets are supplied as biconvex tablets available in 1 mg/500 mg (yellow) and 2 mg/500 mg (pink) strengths. Tablets are debossed with the Novo Nordisk (Apis) bull symbol on one side and tablet strength on the other side. The tablets are colored to indicate strength.

1 mg repaglinide/500 mg metformin HCl tablets (yellow)	Bottles of 20	NDC	0169-0093-21
	Bottles of 100	NDC	0169-0093-01
2 mg repaglinide/500 mg metformin HCl tablets (pink)	Bottles of 20	NDC	0169-0092-21
	Bottles of 100	NDC	0169-0092-01

Do not store above 25° C (77° F).

Protect from moisture. Keep bottles tightly closed.

Dispense in tight containers with safety closures.

17 PATIENT COUNSELING INFORMATION

17.1 Physician Instructions

Patients should be informed of the potential risks and advantages of PrandiMet and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, HbA_{1c}, renal function, and hematologic parameters. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development and concomitant administration of other glucose-lowering drugs should be explained to patients and family members. Medication requirements may change during periods of stress such as fever, trauma, infection, or surgery, due to loss of glycemic control. Patients should be advised to seek medical advice promptly.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the *Warnings and Precautions (5.1)*, should be explained to patients. Patients should be advised to discontinue PrandiMet immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of PrandiMet, gastrointestinal symptoms, which are common during initiation of metformin HCl therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Instruct patients to inform their doctor that they are taking PrandiMet prior to any surgical or radiological procedure, as temporary discontinuation of PrandiMet may be required until renal function has been confirmed to be normal *[see Warnings and Precautions (5.1)]*.

Patients should be instructed to take PrandiMet with meals. Doses are usually taken within 15 minutes prior to the meal but the timing can vary from immediately preceding the meal up to 30 minutes before the meal. Patients who skip a meal should be instructed to skip the PrandiMet dose for that meal.

Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving PrandiMet.

17.2 Laboratory Tests

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. Vitamin B_{12} deficiency should be excluded if megaloblastic anemia is detected.

Version: X

PrandiMet® is a registered trademark of Novo Nordisk A/S.

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