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

- **Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure. (5.1)**
- **Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. (5.1)**
- **If acidosis is suspected, discontinue PrandiMet and hospitalize the patient immediately.**

·····RECENT MAJOR CHANGES·····

- Contraindications (4) 05/2010
- Warnings and Precautions, Drug Interactions (5.7) 05/2010

·····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 (2)
- Start with 1 mg/500 mg twice daily unless the patient is already taking higher co-administered doses of repaglinide and metformin HCl (2)
- Do not exceed 10 mg repaglinide /2500 mg metformin HCl daily or 4 mg repaglinide/1000 mg metformin HCl per meal (2)
- Give in divided doses within 15 minutes prior to meals (2)
- Patients who skip a meal should skip the PrandiMet dose for that meal (2)

·····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 renal impairment. (4, 5.2)
- with metabolic acidosis, including diabetic ketoacidosis. (4, 5.1)
- receiving gemfibrozil. (4, 5.7, 7.2, 12.3)

·····WARNINGS AND PRECAUTIONS·····

- Metformin HCl is contraindicated in renal impairment. Assess renal function before initiating PrandiMet and at least annually thereafter, and verify as normal. (4, 5.2)
- Temporarily discontinue PrandiMet in patients receiving iodinated contrast for radiological studies. (5.3)
- Hepatic impairment is associated with lactic acidosis. Recommend not using in patients with hepatic impairment. (5.4)
- Alcohol potentiates the effect of metformin on lactate metabolism. Warn patients against excess alcohol intake. (5.5)
- PrandiMet should not be used in combination with NPH insulin. (5.6)
- Gemfibrozil substantially increases repaglinide exposure. Coadministration of gemfibrozil and PrandiMet is not recommended. (4, 5.7, 7.2, 12.3)
- The repaglinide component can cause hypoglycemia. Initiate PrandiMet at the lowest available dose in patients naive to meglitinide therapy. (5.8)
- Metformin can cause vitamin B_{12} deficiency. Measure hematological parameters annually. (5.9)
- May need to discontinue PrandiMet and temporarily use insulin if glycemic control deteriorates during periods of stress or if there is decreased intake of fluids and food (e.g., infection, surgery). (5.10)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with PrandiMet or any other oral anti-diabetic drug. (5.15)

·····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 1-888-NOVO-444 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

·····DRUG INTERACTIONS·····

- Cationic drugs eliminated by renal tubular secretion may interfere with metformin elimination: use with caution. (7.1)
- Repaglinide is partly metabolized by CYP2C8 and CYP3A4. Use caution in patients taking inhibitors and/or inducers of CYP2C8 and CYP3A4. (7.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate.

If acidosis is suspected, PrandiMet should be discontinued and the patient hospitalized immediately *[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

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.

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:

- Renal impairment (e.g., serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females], or abnormal creatinine clearance) *[see Warnings and Precautions (5.2)]*.
- 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:

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with PrandiMet; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin HCl is very low (approximately 0.03 cases/1,000 patient-years of exposure, with approximately 0.015 fatal cases/1,000 patient-years of exposure). In more than 20,000 patient-years exposure to metformin HCl in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal impairment and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking PrandiMet and by use of the minimum effective dose of PrandiMet. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Treatment with PrandiMet should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, PrandiMet should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, PrandiMet should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking PrandiMet, since alcohol potentiates the effects of metformin HCl on lactate metabolism. In addition, PrandiMet should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure [*see Warnings and Precautions (5.3), (5.5), and (5.10)*].

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also Warnings and Precautions). PrandiMet should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of PrandiMet, gastrointestinal symptoms, which are common

during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking PrandiMet do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling [*see Warnings and Precautions (5.11), (5.14*)].

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking PrandiMet, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin HCl is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery *[see Contraindications (4)]*.

5.2 Assessment of Renal Function

Metformin is substantially excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, patients with renal impairment should not receive PrandiMet. *[see Warnings and Precautions (5.1), Contraindications (4)]*.

Before initiation of therapy with PrandiMet and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal impairment is anticipated, renal function should be assessed more frequently and PrandiMet discontinued if evidence of renal impairment is present *[see Clinical Pharmacology (12.3)]*.

5.3 Radiologic Studies with Intravascular Iodinated Contrast Materials

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin HCl [*see Contraindications(4)*]. Therefore, in patients in whom any such study is planned, PrandiMet should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

5.4 Impaired Hepatic Function

Hepatic impairment has been associated with some cases of lactic acidosis. Therefore, PrandiMet should generally be avoided in patients with hepatic impairment *[see Clinical Pharmacology (12.3)*].

5.5 Alcohol Intake

Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving PrandiMet.

5.6 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)]*

5.7 Drug Interactions

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

5.8 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)]*.

5.9 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.

5.10 Surgical Procedures

Use of PrandiMet should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

5.11 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.

5.12 Use of Concomitant Medications Affecting Renal Function or Metformin Disposition

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion *[see Drug Interactions (7.1)]* should be used with caution.

5.13 Hypoxic States

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients receiving PrandiMet, the drug should be promptly discontinued.

5.14 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.

5.15 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

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.

6.2 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 Diarrhea Nausea	9 (33) 5 (19) 4 (15)	13 (48) 8 (30) 2 (7)	10 (36) 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)]*.

6.3 Postmarketing Experience

Repaglinide

The following additional adverse reactions have been identified during postapproval use of repaglinide. 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.

Postmarketing experience with repaglinide includes infrequent reports of the following adverse events; alopecia, hemolytic anemia, pancreatitis, Stevens-Johnson Syndrome, and severe hepatic dysfunction including jaundice and hepatitis.

7 DRUG INTERACTIONS

7.1 Cationic Drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Careful patient monitoring and dose adjustment of PrandiMet and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system *[see Clinical Pharmacology (12.3)]*.

7.2 CYP2C8 and CYP3A4 Inhibitors/Inducers

Repaglinide is metabolized by CYP2C8 and to a lesser extent by CYP3A4. Drugs that inhibit 2C8 (gemfibrozil, trimethoprim), 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 (5.7) 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. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Careful monitoring of glucose control is essential in these patients.

Animal reproduction studies have not been conducted with PrandiMet. It is not known whether PrandiMet or its individual components can cause fetal harm when administered to a pregnant woman. PrandiMet should be given to a pregnant woman only if clearly needed.

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, because aging is associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, dose adjustment of PrandiMet should be based on a careful assessment of renal function *[see Warnings and Precautions (5.1 and 5.2), Contraindications (4), Clinical Pharmacology(12.3)]*.

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

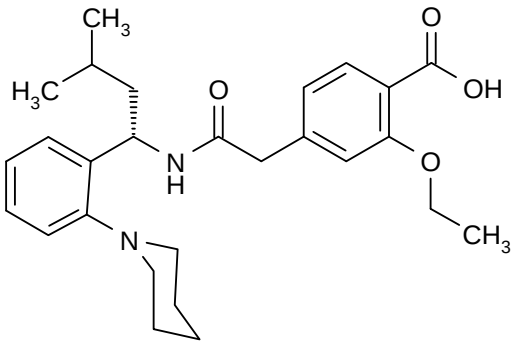
Overdose of metformin HCl has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin HCl has been established. Lactic acidosis has been reported in approximately 32% of metformin HCl overdose cases *[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.

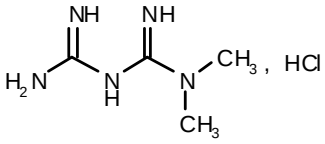
Repaglinide, S(+)2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid, is chemically unrelated to the oral sulfonylurea insulin secretagogues. Repaglinide is a white to off-white powder with molecular formula C_{27} H_{36} N_2 O_4 and a molecular weight of 452.6 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 (V_{ss}) 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

PrandiMet

Because PrandiMet contains metformin HCl, it should not be used in patients with renal impairment [*see Contraindications (4); Warnings and Precautions (5.2)*].

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 (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Impairment

PrandiMet

PrandiMet should be avoided in patients with hepatic impairment *[see Warnings and Precautions (5.4)]*.

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	**C_{max}**
Clarithromycin*	250 mg BID	4 days	40% ↑	67% ↑
Cyclosporine	100 mg [5]	1 day	2.5 fold ↑	1.8 fold ↑
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

↑ 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 HbA1c 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 HbA1c 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.

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.

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

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