PrandiMet®
(repaglinide/metformin HCl) tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed for use of PrandiMet safely and effectively. See full prescribing information for PrandiMet®.

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

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**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.

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**CONTRAINDICATIONS**

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

**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)

**DOSEAGE 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)

**DOSEAGE FORMS AND STRENGTHS**

Tablets:
- 1 mg repaglinide/500 mg metformin HCl (3)
- 2 mg repaglinide/500 mg metformin HCl (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. Co-administration 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 naïve to meglitinide therapy. (5.8)
- Metformin can cause vitamin B12 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)

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**HOW SUPPLIED/STORAGE AND HANDLING**

- Catonic 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)

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**PATIENT COUNSELING INFORMATION**

See 17 for PATIENT COUNSELING INFORMATION

**Revised: 4/2012**

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*Sections or subsections omitted from the full prescribing information are not listed.
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, myalgia, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated lactate blood level.

If acidosis is suspected, PrandiMet® should be discontinued and the patient hospitalized immediately [see Warnings and Precautions (5.1)].

5 Warnings and Precautions
5.1 Lactic Acidosis
Lactic acidosis is 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 hypoxia (eg, myocardial ischemia, renal failure, hypoxemia, hypovolemia, hyperpyrexia, sepsis, peritoneal dialysis, or surgery).

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 impeded as the cause of lactic acidosis, metformin plasma levels >5 mg/L are generally found.

The reported incidence of lactic acidosis in patients receiving metformin HCl is very low (approximately 0.003 cases/1,000 patient-years of exposure, with approximately 0.015 total cases/100,000 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 impairment in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with concomitant heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxia, are at increased risk of lactic acidosis. 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 metformin HCl. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function.

Treatment with PrandiMet® should not be initiated in patients 85 years of age or older unless they have been previously treated with a meglitinide alone or with a nonmetformin antihyperglycemic agent. In addition, PrandiMet® should be promptly withdrawn in the presence of any condition associated with hyperpyrexia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the capacity of patients to metabolize metformin, PrandiMet® should generally be avoided in patients with clinical/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 intravenous radiocontrast study and for any surgical procedure [see Warnings and Precautions (5.3, 5.5, and 5.10)].

The onset of lactic acidosis is often subtle, and accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated lactate blood level. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking a clear cause or in whom development of renal impairment is anticipated. PrandiMet® should be stopped immediately and managed.

6.1 Most Frequently Observed Adverse Reactions
Gastrointestinal System Disorder
Gastrointestinal reactions (eg, diarrhea, nausea, vomiting) are the most common adverse reactions (> 5% in Table 1) occurring in a 6-month randomized study of repaglinide added to metformin HCl in patients with type 2 diabetes. In the clinical trial comparing repaglinide and metformin HCl alone, the most common adverse reactions (≥ 1% in Table 1) occurring in patients treated with repaglinide monotherapy were headache (9%), upper respiratory tract infection (3%), and nasopharyngitis (3%).

1.8% for both treatments, with an incidence of chest pain of 1.8% for repaglinide and 1.7% for metformin HCl doses.

In a randomized study of repaglinide added to metformin HCl in patients with type 2 diabetes, the most common adverse reactions (≥ 5%) with metformin HCl treatment 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 Impaired Glycemic Control on Metformin HCl/Monotherapy
Table 2 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 2: Adverse Reactions Reported in Patients Receiving Combination Therapy in ≥ 10% of Patients

These patients were not those with severe hypoglycemia (hypoglycemia requiring assistance of another person) who were excluded from the analysis.

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 1.7% for sulfonylurea drugs. The incidence of uncontrolled angina was 1.3% for patients on repaglinide and 1.8% for those on sulfonylurea drugs. The incidence of severe angina was 0.3% for patients on repaglinide and 0.1% for those on sulfonylurea drugs.

5.9 Vitamin B12 Levels
In controlled clinical trials of metformin HCl of 28 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. This finding, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin HCl or vitamin B12 supplementation. Measurement of hematocrit 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 B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, vitamin B12 supplementation at 2- to 3-year intervals may be useful.

6 ADVERSE REACTIONS
6.1 Most Frequently Observed Adverse Reactions

Adverse reactions reported in patients receiving combination therapy in ≥ 10% of patients receiving combination therapy

Headache 9 (33) 1 (4) 27
Diabetes N (%)
N (%)
N (%)
No. of Patients Exposed 27 28 28
Gastrointestinal System Disorder 9 (33) 13 (48) 10 (36)
Diabetes 5 (19) 8 (28) 7 (27)
Nausea 4 (15) 2 (7) 4 (14)
Abnormal Laboratory Findings 9 (33) 6 (21) 3 (11)
Hypoglycemia** 6 (22) 4 (15) 3 (11)
Upper Respiratory Tract Infection 3 (11) 3 (11) 3 (11)
sion, abnormal electrocardiogram, myocardial infarction, arrhythmias, and palpitations) was 51% and not different between repaglinide and the comparator drugs.

The incidence of total serious cardiovascular adverse events, including ischemia, was higher for repaglinide (51/236 or 4%) than for sulfonfonylureas (3/468 or 0.7%). In controlled clinical trials, nausea was a common adverse effect. Two patients treated with repaglinide had changes in hepatic function tests.

No patients treated with repaglinide had a change in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or total bilirubin.

B. Clinical Pharmacology (12)

1. Pharmacokinetics

(a) Absorption and Bioavailability

Repaglinide:

After oral administration of a single 850 mg tablet of metformin HCl with food, the area under the plasma concentration-time curve (AUC) was increased by approximately 25%, and the peak plasma concentration (Cmax) was increased by approximately 35%.

Metformin:

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 500 mg to 1,500 mg and 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 oral slightly alters the absorption of metformin, as shown by a 35% lower peak plasma concentration (Cmax), a 21% lower area under the plasma concentration-time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (Tmax) 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.

(b) Distribution

Repaglinide:

After intravenous administration 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:

The apparent volume of distribution (V/F) following single oral dose of 850 mg averaged 238 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses, levels of metformin in erythrocytes are approximately 3 times greater than in serum or plasma. Metformin concentrations in erythrocytes are maintained for 18-24 hours and are generally <1 µg/L. During controlled clinical trials, maximum plasma metformin levels did not exceed 5 µg/mL, even at maximum doses.

(c) Metabolism and Elimination

Repaglinide: Complete biotransformation by oxidative biotransformation and direct conjugation with glucuronic acid after either an intravenous or oral dose. The major metabolites are an oxidized dicarboxylic acid (M1), the aromatic amine (M1), and the acyl glucuronide (M2). The cytochrome P-450 enzyme system, specifically CYP2C8 and CYP3A, have been found 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 1C-repaglinide as a single oral dose, approximately 96% of the radioactivity was recovered in the feces and approximately 4% in the urine. Only 0.1% of the dosing was excreted in the urine as parent compound. The major metabolite (M1) accounted for 55% 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: Intravenous single-dose studies in normal subjects demonstrate that a significant fraction of the dose is unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in human or biliary excretion). Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular excretion is the major route of metformin elimination. Following oral administration, approximately 65% of the absorbed dose is eliminated via the renal route within the first 24 hours. In the plasma, elimination half-life is approximately 6.8 hours, and the elimination half-life is approximately 11 hours, suggesting that the excretion mass may be a component of distribution.
### 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 carcinogenicity, mutagenicity, 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 200 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 maximum recommended human daily dose of 2000 mg of metformin HCl component of PrandiMet® on a mg/kg 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 maximum recommended human daily dose of 2000 mg of metformin HCl component of PrandiMet® on a mg/kg 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 aberration test (human lymphocytes). Results in the in vivo micronucleus tests were also negative.

In a 16-week fertility study in rats at doses up to 800 mg/kg/day, the incidences of benign uterine polyposis were increased in female rats at 300 mg/kg/day (which is approximately 12 times the maximum recommended human daily dose of 2000 mg of metformin HCl monotherapy arm on a mg/kg basis). However, the Incidence was determined to be due to the drug-related effect of metformin HCl at the highest dose level.

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 care practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. If 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 B12 deficiency should be excluded if macrocytic anemia is detected.

### Table 3: Effect of Other Drugs on AUC and Cmax of Metformin

<table>
<thead>
<tr>
<th>Drug Interaction</th>
<th>Drug</th>
<th>AUC</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin HCl</td>
<td>Metformin HCl</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Metformin HCl</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Insulin</td>
<td>Metformin HCl</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Metformin HCl</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Table 4: Effect of Other Drugs on AUC and Cmax of Repaglinide

<table>
<thead>
<tr>
<th>Drug Interaction</th>
<th>Drug</th>
<th>AUC</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin HCl</td>
<td>Metformin HCl</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
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<td>Metformin HCl</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Insulin</td>
<td>Metformin HCl</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Metformin HCl</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Table 6: Effect of Metformin or Repaglinide on AUC and Cmax of Other Drugs

<table>
<thead>
<tr>
<th>Other Drug</th>
<th>AUC</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glimepiride</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Insulin</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### 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, HbA1C, renal function, and hematologic parameters. The risks of hypo- and hyperglycemia, 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 care practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. If 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.

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