Drug-Drug Interactions:
Drug interaction studies performed in healthy volunteers showed that repaglinide had no clinically relevant effect on the pharmacokinetics of concomitantly administered drugs, except as noted.

CYP2C8 and CYP3A4 Inducers/Inhibitors
Sulfonamides: Co-administration of metformin (1000 mg) and a single dose of 0.5 mg Repaglinide resulted in a 20% increase in metformin AUC and Cmax, and a 20% decrease in repaglinide AUC and Cmax.

Antacids: Co-administration of a single 20 mmol hydrochloric acid dose (in 80 mL water) with a 0.5 mg dose of Repaglinide resulted in a 21% decrease in repaglinide AUC and a 22% decrease in Cmax.

Laxatives: Co-administration of a single 40 mg dose of lactulose resulted in a 15% increase in repaglinide AUC and a 16% decrease in Cmax.

Myelosuppressants: Co-administration of cyclophosphamide and single dose of 0.5 mg Repaglinide resulted in a 12% decrease in repaglinide AUC and a 13% decrease in Cmax.

Cyclosporine: Co-administration of cyclosporine (50 mg/kg) and a single dose of 0.5 mg Repaglinide resulted in a 10% decrease in repaglinide AUC and a 11% decrease in Cmax.

Cyclosporine: Co-administration of cyclosporine (50 mg/kg) and a single dose of 0.5 mg Repaglinide resulted in a 10% decrease in repaglinide AUC and a 11% decrease in Cmax.


table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients with type 2 diabetes*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td><strong>AUC</strong></td>
</tr>
<tr>
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</tbody>
</table>

Subjects with FPG above 270 mg/dL were withdrawn from the study.

Pioglitazone dose: fixed at 30 mg/day. Median/mean final dose: 6 mg/day for combination and 12 mg/day for monotherapy.

A combination therapy regimen of Repaglinide and pioglitazone was compared to monotherapy with either agent alone in a 24-week trial that enrolled 252 patients previously treated with sulfonylurea or metformin monotherapy (HbA1c >7%).

Mean changes from baseline associated with combination therapy was greater than that of Repaglinide monotherapy.
The frequency of hypoglycemia is greater in patients with type 2 diabetes who have not been previously treated with oral blood glucose-lowering drugs (sulfonylureas) or whose HbA1c is less than 8%. Repaglinide should be administered with meals to lessen the risk of hypoglycemia.

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 loss of glycemic control may occur. At such times, it may be necessary to temporarily discontinue or to reduce the dose of Repaglinide and administer insulin or other glucose-lowering agents.

Pediatric Use

No controlled studies of Repaglinide in children have been conducted. Use in pediatric patients is not recommended.

Drug Interactions

Doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to 2 hours after the meal. Patients who eat a meal (or add a meal) should be instructed to skip (or add) a dose for that meal.

A pharmaceuticals should be observed closely for loss of glycemic control. Postprandial glucose level testing may be clinically helpful in patients whose pre-meal blood glucose levels are satisfactory but whose overall glycemic control (HbA1c) is inadequate.

Laboratory Tests

In vivo data from a study that evaluated the co-administration of a cytochrome P450 enzyme 3A4 inhibitor, clarithromycin, with Repaglinide resulted in a clinically significant increase in repaglinide plasma concentrations. Drugs that are known to inhibit CYP3A4 include antifungal agents like ketoconazole, itraconazole, and antibacterial agents like erythromycin. Drugs that are known to inhibit CYP3A4 include the following: trimethoprim, gemfibrozil, methadone, and mexiteline. These increases in repaglinide plasma levels may necessitate a Repaglinide dose adjustment. See CLINICAL PHARMACOLOGY section, Drug-Drug Interactions.

In patients with renal impairment, Repaglinide tablets, USP, 2 mg are available in the following forms: Pink, round, biconvex tablets, in nitrogen-purged blisters, in a box of 100 tablets.

Mean change in weight from baseline was +4.9 kg for Repaglinide-thiazolidinedione therapy. There were reports of hypoglycemia which occurred in 16% of Repaglinide patients, 20% of glyburide patients, and 19% of glipizide patients. The most common adverse events leading to withdrawal of patients were cough (3%), headache (2%), nausea (2%), and vomiting (1%). In studies comparing Repaglinide with insulin, the most common adverse events were hypoglycemia (16%) and injection site reactions (6%).

In a study comparing Repaglinide with glipizide, the incidence of hypoglycemia was 20% in Repaglinide patients, 28% in glyburide patients, and 23% in glipizide patients. The most common adverse events leading to withdrawal were hypoglycemia (15%), headache (7%), and nausea (7%). Repaglinide was not associated with excess mortality when compared to the rates of the comparator drugs.

In one-year trials comparing Repaglinide to sulfonylurea drugs, the incidence of angina was comparable (18%) for both treatments, with an incidence of chest pain of 18% for Repaglinide and 1.0% for sulfonlurea. The incidence of other selected cardiovascular events (hypertension, abnormal LSGI, myocardial infarction, arrhythmias, and palpitations) was 1% and not different between Repaglinide and the comparator drugs.

In the context of these adverse cardiovascular events, including ischemia, which was higher for repaglinide (4%) than for sulfonlurea drugs (3%) in controlled comparator trials. However, in long-term clinical trials, repaglinide treatment was not associated with excess mortality when compared to the rates observed with other hypoglycemic agent therapies.

Summary of Serious Cardiovascular Events (% of total patients with events in Trials Comparing Repaglinide to Sulfonylureas)

**OVERDOSAGE**

In a clinical trial, patients received increasing doses of Repaglinide up to 80 mg a day for 14 days. There were few adverse effects other than those associated with the intended effect of lowering blood glucose. Hypoglycemia did not occur when meals were given with these high doses. Hypoglycemic symptoms without loss of consciousness or neurologic findings were treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring may 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 by hemodialysis.

Severe hypoglycemic reactions with coma, seizures, 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 diluted (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dl.

**DOSAGE AND ADMINISTRATION**

There is no fixed dosage regimen for the management of type 2 diabetes with Repaglinide.

The patient’s blood glucose should be monitored periodically to determine the effective dose for the patient; to detect the potential for a significant change in the patient’s overall glycemic control; and to detect secondary failure, i.e., loss of an adequate blood glucose-lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels are of value in monitoring the patient’s longer term response to therapy.

Combination Therapy

If Repaglinide monotherapy does not result in adequate glycemic control, a thiazolidinedione may be added. If thiazolidinedione monotherapy does not provide adequate control, Repaglinide may be added. The starting dose and dose adjustments for Repaglinide combination therapy is the same as for Repaglinide monotherapy. The dose of each drug should be carefully adjusted to determine the minimal dose required to achieve the desired degree of glycemic control. Repaglinide, close monitoring may be indicated for up to two weeks or longer.

**HOW SUPPLIED**

Repaglinide tablets, USP. 1 mg are available in the following forms: Yellow, round, biconvex tablets, debossed with “745” on one side and “C” on the other side.

Bottles of 100 NDC 57664-745-88
Bottles of 500 NDC 57664-745-53
Bottles of 1000 NDC 57664-745-18

Repaglinide tablets, USP, 2 mg are available in the following forms: Pink, round, biconvex tablets, debossed with “747” and “C” on one side and “O” on the other side.

Bottles of 100 NDC 57664-747-88
Bottles of 500 NDC 57664-747-53
Bottles of 1000 NDC 57664-747-18

Repaglinide tablets, USP, 3 mg are available in the following forms: Pink, round, biconvex tablets, debossed with “749” and “C” on two sides.

Bottles of 100 NDC 57664-749-88
Bottles of 500 NDC 57664-749-53
Bottles of 1000 NDC 57664-749-18

Store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature].

Protect from moisture.
Keep bottles tightly closed.
Dispense in tight containers with safety closures.

Manufactured by: Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512

Issued: 01/92

Detroit, MI 48202