Repaglinide – *Prandin*®, Novo Nordisk

Development:[1-4]

Diabetes mellitus is actually a variety of metabolic disorders characterized most commonly by hyperglycemia. The National Institutes of Diabetes and Digestive Kidney Diseases (NIDDK) estimates that as many as 16 million Americans have diabetes. Currently 8 million diabetics have been diagnosed and the majority of these (7.5 million) have the non-insulin-dependent or type 2 form of the disease (NIDDM, or late-onset diabetes), while an estimated 500,000 diabetics suffer from the insulin-dependent or type 1 form of the disease (IDDM). The hyperglycemia associated with type 2 diabetes is caused by defects in glucose-induced insulin secretion, impaired insulin sensitivity in peripheral tissues and hepatic insulin resistance. These defects in combination result in decreased glucose uptake, hyperglycemia and other metabolic abnormalities characteristic of the disease.

The chronic hyperglycemia associated with type 1 and type 2 diabetes is directly associated with a greater risk of mortality and the development of a variety of debilitating pathologies including cardiovascular and peripheral vascular disease, stroke, visual impairment and blindness, nephropathy and neuropathy. Studies such as the Diabetes Control and Complications Trial (DCCT) have demonstrated that careful glycemic control can significantly reduce the risk for development and progression of a number of these pathologies. Although diet and exercise remain the primary initial treatment for patients with type 2 diabetes, it has been established that more than 90% of these patients cannot maintain long-term glycemic control with this approach alone. Traditionally when diet and exercise failed, oral hypoglycemic agents - particularly drugs of the sulfonylurea class - are added to the treatment regimen. These agents including *Orinase, Tolinase, Glucotrol, Diabeta* work primarily to stimulate insulin production. However, prolonged use of the sulfonylureas frequently leads to desensitization of pancreatic beta-cells and loss of efficacy. Hence, about half of all type 2 diabetics are required to administer insulin on a daily basis. Also, hypoglycemic is a common adverse reaction with the sulfonylureas, and the long duration of action of many of these agents significantly increases the risk for hypoglycemia. Furthermore, since many of the current sulfonylureas are eliminated renally, the risk of hypoglycemia is increased in geriatric patients and those with kidney dysfunction.

The continued high morbidity and mortality associated with type 1 and type 2 diabetes suggest that traditional sulfonylurea and insulin therapies are less than satisfactory. In recent years a number of alternative therapies for type 2 diabetes have been developed, focusing on drugs with novel mechanisms of actions such as the biguanides (*Glucophage*), the alpha-glucosidase inhibitors (*Precose*Ò, *Glyset*Ò) and, most recently, the thiazolidinedione troglitazone *(Rezulin*Ò). Metformin reduces the hepatic secretion and increases the tissue uptake of glucose. It is as effective as the sulfonylureas and does not cause hypoglycemia. It may, however, cause lactic acidosis, particularly in patients with renal impairment. The alpha-glucosidase inhibitors *Precose* and *Glyset* delay the absorption of carbohydrates from the small intestine, and also do not cause hypoglycemia. Unfortunately these drugs have only a modest effect on blood glucose levels and may cause hepatotoxicity. Furthermore, both metformin and the alpha-glucosidase inhibitors may cause abdominal discomfort and other GI tract side effects. Troglitazone was the first drug on the market that decreased insulin resistance, and generally is used with a sulfonylurea, metformin or

insulin for insulin-resistance patients. The utility of troglitazone is limited by its potential hepatotoxicity, and this has resulted in its removal from the market abroad. Thus there remains in interest in developing novel antidiabetic agents with enhanced efficacy and greater safety and tolerability.

Repaglinide, the newest antidiabetic agent, is a novel oral blood glucose-lowering agent that is distinct from all other antidiabetic agents in its chemical structure, mechanism of binding to target channels in beta-cells, and mode of elimination. This agent has several desirable properties including a rapid onset and short duration of action and metabolism, and excretion by non-renal routes. Furthermore, it can work synergistically with other antidiabetic drugs such as metformin in patients whose hyperglycemia is not controlled by monotherapy. Thus repaglinide may offer some advantages in therapy over traditional and even newer antidiabetic drug therapies.

Pharmacology and Therapeutics:[4-8]

Repaglinide is a non-sulfonylurea hypoglycemic agent that consists structurally of the non-sulfonylurea moiety of glyburide. Mechanistically repaglinide is similar to the sulfonylureas in that it interacts with binding sites on ATP-dependent potassium channels in the beta-cell membrane. These sites are distinct from those involved in sulfonylurea binding. The binding of repaglinide results in potassium channel blockade which depolarizes the beta cell and leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion. Thus the actions of repaglinide are dependent upon functional beta cells in the pancreatic islets. The ion channel mechanism is highly tissue selective with low affinity for heart and skeletal muscle.

The efficacy of repaglinide was demonstrated in three multicenter, placebo-controlled trials involving more than 600 type 2 diabetic patients. In these trials repaglinide was shown to effectively lower fasting blood glucose concentrations (-31%), glycosylated hemoglobin (-0.6%), 2-hour postprandial plasma glucose (-48%) and mean glucose concentration under the 24 hour blood glucose concentration-time profile. Most effects were dose-dependent with minimal efficacy achieved at the 0.5 mg dose, and optimum effectiveness observed in the majority of patients at doses from 2-4 mg. The dosing of repaglinide relative to meal-related insulin release was studied in three trials including 58 patients. Glycemic control was maintained during a period in which the meal pattern (2, 3 or 4 meals per day) and dosing pattern was varied compared with a period of 3 regular meals and 3 doses per day before meals. These studies demonstrated that repaglinide can be administered at the start of a meal, 15 to 30 minutes before the meal with the same blood glucose-lowering effect. In 1-year controlled comparative trials with sulfonylurea hypoglycemics, repaglinide was found to be at least as effective as glyburide and glipazide, and more effective than glipizide using fasting blood glucose and glycosylated hemoglobin as primary measures of efficacy. Also, in this trial mild or moderate hypoglycemia was reported in 16% of the repaglinide patients (1228), 20% of glyburide patients (417) and 19% of glipizide patients (81). Repaglinide was also evaluated in combination with metformin in patients (83) whose blood glucose levels were not adequately controlled by exercise, diet and metformin alone. Combination therapy with repaglinide and metformin resulted in synergistic improvement in glycemic control compared with either repaglinide or metformin monotherapy. Glycosylated hemoglobin levels (HbA1c) were improved by 1.4% unit and fasting plasma glucose (FPG) decreased by an additional 35 mg/dl. Based on the efficacy demonstrated in clinical trials to date, repaglinide is

currently indicated as an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone. It may also be used in combination with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by exercise, diet and either agent alone.

Adverse Reactions:[4-8]

During comparative clinical trials, 13% of repaglinide patients discontinued therapy because of adverse events vs 14% of sulfonylurea patients. Hyperglycemia, hypoglycemia and related symptoms were the most common adverse events resulting in discontinuation, and the incidence of hypoglycemia was slightly lower in the repaglinide treated group (see "Therapeutics" section). It should be noted that with repaglinide, like other antidiabetic drugs, the risk of serious hypoglycemia may be increased in elderly, debilitated or malnourished patients, and those with adrenal, pituitary or hepatic insufficiency. In general, the adverse reaction profile of repaglinide is similar to that noted for the sulfonylurea drugs. In comparative trials, the incidence of individual cardiovascular adverse reactions (hypertension, abnormal ECG, MI, arrhythmias, palpitations) was less than 1% except for chest pain (1.8%) and angina (1.8%), and the overall incidence of such events was not different for repaglinide and the comparator drugs. The incidence of serious cardiovascular adverse events added together, including ischemia, was slightly higher for repaglinide (4%) than for sulfonylurea drugs (3% for glipizide and glyburide). Cardiac ischemic events were 2% for both groups, and deaths from CV events were 0.1% and 0.04%, respectively. Overall, no differences were seen in adverse events between subjects > 65 years of age and those < 65 years old other than the expected age-related increase in cardiovascular events observed for repaglinide and comparator drugs. There also was no increase in frequency or severity of hypoglycemia in older subjects.

Drug Interactions:[4-8]

Currently no clinically significant drug interactions have been reported with repaglinide. However, repaglinide metabolism may be decreased by inhibitors of CYP 3A4 such as the azole antifungal (ketoconazole, miconazole, etc.) and some antibiotics including erythromycin, resulting in increased serum concentrations. Conversely, drugs that induce the CYP 3A4 (i.e. troglitazone, rifampin, barbiturates, carbamazepine) may increase repaglinide metabolism and thereby decrease its antidiabetic the effects when used concurrently. The actions of oral hypoglycemic agents may be potentiated by certain drugs including NSAIDs and other drugs that are highly protein bound such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, MAOIs and beta blockers. Thus patients should be monitored closely for loss of glycemic control when these agents are added to or withdrawn from patients on repaglinide therapy. Also thiazide diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, isoniazid and other drugs that produce hyperglycemia should be used cautiously and with monitoring in patients treated with repaglinide.

Pharmacokinetics:[4-8]

Repaglinide is rapidly and completely absorbed from the GI tract upon oral administration with a mean absolute bioavailability is 56%. After single and multiple oral doses, peak plasma drug levels (C_{max}) occur within 1 hour (T_{max}). When given with food, the mean T_{max} is not altered, but the mean C_{max} and AUC (area under the time/plasma concentration curve) are reported to decrease by 20% and 12.4%, respectively. The volume of distribution for repaglinide at steady state is 31 L, and the total body clearance is 38 L/hr. Protein binding and binding to human serum albumin is estimated at > 98%. Repaglinide is rapidly eliminated from the blood with a half-life of approximately 1 hour. It is completely metabolized by oxidative biotransformation and direct conjugation with glucuronic acid. The major metabolites are an oxidized dicarboxylic acid (M2), the aromatic amine (M1) and the acyl glucuronide (M7). The cytochrome P450 isozyme CYP3A4, is involved in the N-dealkylation of repaglinide to M2 and the further oxidation to M1. None of these metabolites appear to possess significant antidiabetic activity. Within 96 hours after a single oral dose, about 90% is recovered in the feces and approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound and less than 2% of the parent drug is eliminiated in the feces. The major metabolite M2 accounts for 60% of the administered dose. While the AUC ranges 15% to 70% higher in females with type 2 diabetes, this difference does not appear to be reflected in the frequency of hypoglycemic episodes or other adverse events and thus no change in general dosage recommendation appears indicated. Also, both AUC and C_{max} are reported to be higher in patients with reduced renal function. While initial dosage adjustment does not appear to be necessary in the renally impaired, subsequent dose increases should be done with caution in these patients. Patients with impaired liver function may be exposed to higher concentrations of repaglinide and its metabolites than those with normal liver function receiving usual doses. Therefore, this drug should be used cautiously in these patients and longer intervals between dose adjustments allowed to accurately assess response.

Administration and Dosage:[4-8]

Repaglinide is supplied as 0.5 mg, 1 mg and 2 mg unscored tablets. As with other antidiabetic agents, there is no fixed dosage regimen for this drug, but the usual dose range is 0.5 to 4 mg. For patients not previously treated or whose HbA1c is < 8%, the recommended starting dose is 0.5 mg. For patients previously treated with blood glucose-lowering agents and whose HbA1c is ≥ 8%, the initial recommned dose is 1 or 2 mg before each meal. Repaglinide is typically taken within 15 minutes of the meal, but time may vary from immediately preceding the meal to as long as 30 minutes before the meal. Repaglinide may be dosed preprandially 2, 3 or 4 times a day in response to changes in the patient's meal pattern. Dose adjustments are determined by blood glucose response (usually fasting blood glucose) and at least one week should elapse to assess response after each dose adjustment. Typically the preprandial dose is doubled up to 4 mg until satisfactory blood glucose response is achieved. The maximum recommended daily dose is 16 mg. Patient's blood glucose should also be monitored periodically to determine the minimum effective dose for the patient, to detect primary failure (ie, inadequate lowering of blood glucose at the maximum recommended dose of medication); and to detect secondary failure (ie, loss of adequate blood glucose-lowering response after an initial period of effectiveness).

When repaglinide is used to replace therapy with other oral hypoglycemic agents, it may be started the day after the final dose of the other drug is given. When transferred from longer half-life sulfonylureas (eg, chlorpropamide), close monitoring may be indicated for a week or moreto

detect hypoglycemia resulting from overlapping of drug effects. In cases where metformin therapy does not provide adequate control, repaglinide may be added. Also, metformin may be added in cases where repaglinide monotherapy does not result in adequate glycemic control,. The starting dose and dose adjustments for these combination therapies are the same as repaglinide monotherapy, and adjustments should be performed carefully to determine the minimal dose required to achieve the desired therapeutic effect and to avoid hypoglycemic episodes.

References:

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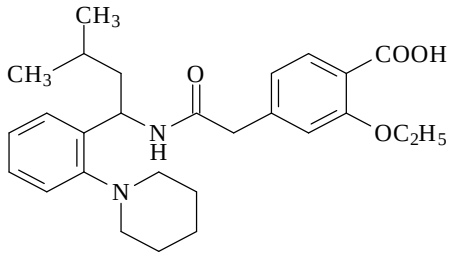
1. Repaglinide (*Prandin®*) produces its therapeutic effects by interaction with:

   (A) *Pancreatic ATP-dependent potassium channels*
   (B) Alpha-glucosidase
   (C) Hepatic Beta-adrenergic receptors
   (D) Insulin receptors

2. The recommended dose range and schedule for repaglinide **(*P**randin®*)** is:

   (A*) 0.5 to 4 mg preprandially from 2-4 times a days*
   (B) 4 to 16 mg once a day
   (C) 0.5 to 4 mg in the morning and evening
   (D) 2 to 8 mg twice a day



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