IMPORTANT INFORMATION

September, 2003

NOTICE: PRANDIN® (repaglinide tablets) PACKAGE INSERT UPDATE

A drug-drug interaction between repaglinide (PRANDIN), a short-acting insulin secretagogue, and gemfibrozil (Lopid) a lipid-lowering agent used to treat dyslipidemia, was recently reported in a publication by Niemi et al.[1] The results of this study indicate that co-administration of gemfibrozil with PRANDIN in healthy volunteers resulted in a significant increase in repaglinide blood levels. Co-administration of itraconazole, an antifungal, with gemfibrozil and PRANDIN further increased such effects. Itraconazole in combination with PRANDIN exhibited less pronounced effects than gemfibrozil.

Changes in repaglinide pharmacokinetics were attributed to inhibition of the cytochrome P-450 enzyme system by gemfibrozil and itraconazole. Changes in the blood glucose concentration were also affected by these concomitant medications, with enhanced and prolonged pharmacodynamic effects of repaglinide. While the study was done in healthy volunteers, Novo Nordisk considers these results to be important, as an increased risk of hypoglycemia cannot be ruled out for patients with type 2 diabetes.

Based upon what is currently known of the metabolism of other lipid-lowering fibrate derivates, a similar interaction between PRANDIN and other agents within the class is not expected.

Through this announcement, Novo Nordisk is informing all general practice and family practice physicians, internists, endocrinologists, and retail and hospital pharmacies of a change in the PRANDIN package insert regarding this drug interaction. Affected sections are shown on the following page. The new text is underlined.

If you require further information, please contact our Drug Information Department at 1-800-727-6500.

Sincerely,

Olga M. Santiago, M.D.
Executive Director
Medical Affairs

[1] Niemi M, Backman JT, Neuvonen M, Neuvonen PJ. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. Diabetologia, 2003; 46 (3): 347-351.

Novo Nordisk Pharmaceuticals Inc. 100 College Road West Princeton, NJ, 08540 USA Telephone: 609-987-5800 Internet: http://www.novonordisk-us.com/

CHANGES TO THE PRANDIN PACKAGE INSERT

CLINICAL PHARMACOLOGY

Drug-Drug Interactions:

Drug interaction studies performed in healthy volunteers show that PRANDIN had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline, or warfarin. Co-administration of cimetidine with PRANDIN did not significantly alter the absorption and disposition of repaglinide.

Additionally, the following drugs were studied in healthy volunteers with co-administration of PRANDIN. Listed below are the results:

Gemfibrozil and Itraconazole: Co-administration of gemfibrozil (600 mg) and a single dose of 0.25 mg PRANDIN (after 3 days of twice-daily 600 mg gemfibrozil) resulted in an 8.1-fold higher repaglinide AUC and prolonged repaglinide half-life from 1.3 to 3.7 hr. Co-administration with itraconazole and a single dose of 0.25 mg PRANDIN (on the third day of a regimen of 200 mg initial dose, twice-daily 100 mg itraconazole) resulted in a 1.4-fold higher repaglinide AUC. Co-administration of both gemfibrozil and itraconazole with PRANDIN resulted in a 19-fold higher repaglinide AUC and prolonged repaglinide half-life to 6.1 hr. Plasma repaglinide concentration at 7 h increased 28.6-fold with gemfibrozil co-administration and 70.4-fold with the gemfibrozil-itraconazole combination. (see **PRECAUTIONS, Drug-Drug Interactions**).

Ketoconazole: Co-administration of 200 mg ketoconazole and a single dose of 2 mg PRANDIN (after 4 days of once daily ketoconazole 200 mg) resulted in a 15% and 16% increase in repaglinide AUC and Cmax, respectively. The increases were from 20.2 ng/mL to 23.5 ng/mL for Cmax and from 38.9 ng/mL*hr to 44.9 ng/mL*hr for AUC.

PRECAUTIONS

Drug-Drug Interactions

In vitro data indicate that repaglinide metabolism may be inhibited by antifungal agents like ketoconazole and miconazole, and antibacterial agents like erythromycin (cytochrome P-450 enzyme system 3A4 inhibitors). Drugs that induce the cytochrome P-450 enzyme system 3A4 may increase repaglinide metabolism; such drugs include rifampin, barbiturates, and carbamezapine. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions**.

In vivo data from a study that evaluated the co-administration of a cytochrome P-450 enzyme inhibitor, clarithromycin, with PRANDIN resulted in a clinically significant increase in repaglinide plasma levels. This increase in repaglinide plasma levels may necessitate a PRANDIN dose adjustment. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions**.

In vivo data from a study that evaluated the co-administration of gemfibrozil with PRANDIN in healthy subjects resulted in a significant increase in repaglinide blood levels. **Patients taking PRANDIN should not start taking gemfibrozil; patients taking gemfibrozil should not start taking PRANDIN. Concomitant use may result in enhanced and prolonged blood glucose-lowering effects of repaglinide. Caution should be used in patients already on PRANDIN and gemfibrozil - blood glucose levels should be monitored and PRANDIN dose adjustment may be needed. Rare postmarketing events of serious hypoglycemia have been reported in patients taking PRANDIN and gemfibrozil together. Gemfibrozil and itraconazole had a synergistic metabolic inhibitory effect on PRANDIN. Therefore, patients taking PRANDIN and gemfibrozil should not take itraconazole.** See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions.**