IMPORTANT SAFETY INFORMATION ON THE CONCOMITANT USE OF GLUCONORM® (REPAGLINIDE) AND GEMFIBROZIL

July 17, 2003

Dear Healthcare Professional:

Re: Important Safety Information on the concomitant use of GlucoNorm® (repaglinide) and gemfibrozil.

The purpose of this letter is to provide important information regarding a contraindication for the concomitant use of GlucoNorm® (repaglinide) and gemfibrozil.

- The **concomitant** use of **GlucoNorm®** (repaglinide) and **gemfibrozil** is **contraindicated**.
- The blood glucose-lowering effects of GlucoNorm® (repaglinide) may be **markedly enhanced and prolonged when administered together with gemfibrozil**.
- Patients using **GlucoNorm® (repaglinide) and gemfibrozil at the same time may be at risk of severe and prolonged hypoglycemia**.

A study was recently published in Diabetologia [2003;46(3)347-351] by Niemi *et al*. The study, that was designed to address the pharmacokinetic interaction between GlucoNorm®(repaglinide) , a short-acting insulin secretagogue marketed by Novo Nordisk and gemfibrozil, a lipid-lowering agent for treatment of dyslipidaemia, was sponsored independently from the manufacturers involved. When administered concomitantly with gemfibrozil, GlucoNorm® (repaglinide) was found to have a markedly enhanced and prolonged glucose-lowering effect in healthy volunteers. By extrapolation, patients using GlucoNorm® (repaglinide) and gemfibrozil at the same time may be at risk of severe and prolonged hypoglycemia, therefore the concomitant use of Gluconorm® (repaglinide) and gemfibrozil is now contraindicated.

Niemi *et al*. reported significantly altered pharmacokinetic properties of repaglinide following co-administration with gemfibrozil in healthy volunteers. The area under the curve (AUC) was increased 8.1-fold (range 5.5- to 15-fold; $p < 0.001$) and the elimination half life ($t_{½}$) was prolonged from 1.3 hours to 3.7 hours ($p < 0.001$). These changes are thought to be due to the inhibition of CYP2C8 by gemfibrozil as evidenced by decreases in blood glucose levels that were proportional to the dose of gemfibrozil.

In the Novo Nordisk international safety database we have identified five serious reports of hypoglycemia during treatment with repaglinide where the patient concomitantly received gemfibrozil. All five reports were spontaneous (3 reports from the United States and 2 from France), and were received between April 1999 and February 2003. No spontaneous reports were received from Canadian sources regarding combined use of GlucoNorm® (repaglinide) and gemfibrozil.

In light of this information, patients receiving GlucoNorm® (repaglinide) and gemfibrozil may be at risk of severe or prolonged hypoglycemia (low blood sugar). Therefore, patients currently receiving GlucoNorm® (repaglinide) with gemfibrozil should be reassessed by their physician and alternative combination treatment considered under close monitoring of diabetic status.

Patients being treated with GlucoNorm® (repaglinide) should note receive gemfibrozil and patients already taking gemfibrozil should discontinue this drug before being prescribed repaglinide.

Due to the significance of these results from the referenced article, Novo Nordisk will add this new safety information to the Canadian Product Monograph. Health care professionals are advised to review the Product Monograph when prescribing GlucoNorm® (repaglinide) in the future.

It should be noted that reporting rates determined on the basis of spontaneously reported post-marketing adverse events are generally presumed to underestimate the risk associated with a drug treatment.

The identification, characterization, and management of drug-related adverse events are dependent on the active participations of healthcare professionals in adverse drug reaction reporting programmes. Healthcare professionals are asked to report any suspected adverse reactions in patients receiving GlucoNorm® (repaglinide) directly to Novo Nordisk Canada Inc. at the following address:

Novo Nordisk Canada Inc.
c/o Medical and Scientific Affairs Department
2700 Matheson Blvd. East
3rd Floor, West Tower
Mississauga, ON L4W 4V9
Tel: (905) 629-4222
Toll: 1-800-465-4334

Your professional commitment in this regard has an important role in protecting the well-being of your patients by contributing to early signal detection and informed drug use.

Sincerely,
Novo Nordisk Canada Inc.

original signed by

Alan Davis, Ph.D., MBA
Director,
Medical and Scientific Affairs

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Any suspected adverse reactions can also be reported to:

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0201C2
OTTAWA, Ontario, K1A 1B9
Tel: (613) 957-0337 or Fax: (613) 957-0335
Toll free for consumers and health professionals:
Tel: 866 234-2345, Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

The AR Reporting Form and the AR Guidelines can be found on the TPD web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.