The European Agency for the Evaluation of Medicinal Products
Post-authorisation evaluation of medicines for human use

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EMEA PUBLIC STATEMENT ON REPAGLINIDE (NovoNorm/Prandin) CONTRAINDICATION OF CONCOMITANT USE OF REPAGLINIDE AND GEMFIBROZIL

The EMEA wishes to inform the public about an interaction between repaglinide, a medicine used to lower blood sugar in diabetic patients, and gemfibrozil, a lipid-lowering agent.

A recent scientific publication[1] indicates that the blood glucose-lowering effect of repaglinide may be markedly enhanced and prolonged when administered together with gemfibrozil, with an increased risk of severe hypoglycaemia. In addition, 5 reports of serious hypoglycaemic episodes in patients using repaglinide and gemfibrozil at the same time have been received. The Agency's Committee for Proprietary Medicinal Products (CPMP) has therefore decided to contraindicate the concomitant use of repaglinide and gemfibrozil.

There are two repaglinide products authorised in the European Union, NovoNorm and Prandin, authorised in August 1998 and January 2001 respectively. The Marketing Authorisation Holder for both products is Novo Nordisk.

Repaglinide is indicated in patients with Type 2 diabetes (Non Insulin-Dependent Diabetes Mellitus (NIDDM)) whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. Repaglinide is also indicated in combination with metformin in Type 2 diabetes patients who are not satisfactorily controlled on metformin alone. Repaglinide is currently marketed in all EU Member States (except Portugal), Norway and Iceland.

The EMEA wishes to point out the following important safety information to physicians:

- In view of a documented interaction and risk of hypoglycaemia, the concomitant use of repaglinide and gemfibrozil is contraindicated.
- Patients already receiving repaglinide with gemfibrozil should be reviewed and alternative combination treatment considered under close monitoring of diabetic status.

Information for patients taking repaglinide:

- If you are on repaglinide (NovoNorm, Prandin) for diabetes and are also given gemfibrozil you may be at risk of severe or prolonged hypoglycaemia (low blood sugar). You should therefore contact your doctor as you may require adjustment in your medication.

[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.

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As an urgent measure, the prescribing and patient information of repaglinide have been modified through a rapid procedure at the request of the Marketing Authorisation Holder. Relevant changes to the product information are indicated below. The complete revised product information is available in the European Public Assessment Report of NovoNorm and Prandin published on the EMEA Website.

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CHANGES INTRODUCED
TO INFORMATION FOR PATIENTS AND PRESCRIBERS

NovoNorm 0.5 mg tablet as relevant example

INFORMATION TO PRESCRIBERS (SUMMARY OF PRODUCT CHARACTERISTICS):

4.3 Contraindications

- Known hypersensitivity to repaglinide or any of the excipients in NovoNorm
- Type 1 diabetes (Insulin-Dependent Diabetes Mellitus: IDDM), C-peptide negative
- Diabetic ketoacidosis, with or without coma
- Pregnancy and lactation (Section 4.6)
- Children <12 years of age
- Severe hepatic function disorder
- **Concomitant use of gemfibrozil (see section 4.5 Interaction with other medicinal products and other forms of interaction)**

4.5 Interaction with other medicinal products and other forms of interaction

A number of drugs are known to influence glucose metabolism, possible interactions should therefore be taken into account by the physician:

The following substances may enhance **and/or prolong** the hypoglycaemic effect of repaglinide: **Gemfibrozil, clarithromycin, itraconazole, ketokonazole**, other antidiabetic agents, monoamine oxidase inhibitors (MAOI), non selective beta blocking agents, angiotensin converting enzyme (ACE)-inhibitors, salicylates, NSAIDS, octreotide, alcohol, and anabolic steroids.

Co-administration of gemfibrozil, an inhibitor of CYP2C8, increased the repaglinide AUC 8.1-fold and C_{max} 2.4-fold in healthy volunteers. Half-life was prolonged from 1.3 hr to 3.7 hr, and plasma repaglinide concentration at 7 hr was increased 28.6-fold by gemfibrozil. The concomitant use of gemfibrozil and repaglinide is contraindicated (see section 4.3 Contraindications).

The effect of ketoconazole, a prototype of potent and competitive inhibitors of CYP3A4, on the pharmacokinetics of repaglinide has been studied in healthy subjects. Co-administration of 200 mg ketoconazole increased the repaglinide (AUC) by 15% and C_{max} by 16%. **Co-administration of 100 mg itraconazole has also been studied in healthy volunteers, and increased the AUC by 40%. No significant effect on the glucose level in healthy volunteers was observed.** In an interaction study in healthy volunteers, co-administration of 250 mg clarithromycin, **a mechanism-based inhibitor of CYP3A4**, increased the repaglinide (AUC) by 40% and C_{max} by 67% and increased the mean incremental AUC of serum insulin by 51% and the maximum concentration by 61%. The exact mechanism of this interaction is not clear.

β-blocking agents may mask the symptoms of hypoglycaemia.

Co-administration of other compounds that are metabolised by CYP3A4, such as cimetidine, nifedipine and oestrogen, did not significantly alter the absorption and disposition of repaglinide during multiple dosing in healthy subjects. In an interaction study in healthy volunteers, simvastatin did not alter the exposure to repaglinide, mean C_{max} however, was increased by 25% with a very high variability (95% CI 0.95-1.68). The clinical relevance of this finding is not clear.
In an interaction study in healthy volunteers, rifampicin reduced the repaglinide (AUC) by 25%. The clinical relevance of this finding is not clear.

Repaglinide had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline or warfarin at steady state, when administered to healthy volunteers. Dosage adjustment of these compounds when co-administered with repaglinide is therefore not necessary.

The following substances may reduce the hypoglycaemic effect of repaglinide:
Oral contraceptives, thiazides, corticosteroids, danazol, thyroid hormones and sympathomimetics.

When these medications are administered to or withdrawn from a patient receiving repaglinide, the patient should be observed closely for changes in glycaemic control.

When repaglinide is used together with other drugs that are mainly secreted by the bile like repaglinide any potential interaction should be considered.

INFORMATION TO PATIENTS (PACKAGE LEAFLET):

6. Before you use NovoNorm

NovoNorm should not be used if:

- You have been told you are allergic to repaglinide (the active ingredient in NovoNorm) or any of the ingredients in NovoNorm
- You have Type 1 diabetes (Insulin-Dependent Diabetes Mellitus)
- Diabetic ketoacidosis
- You are below 12 years of age
- You have a severe hepatic disease
- **You use gemfibrozil (a lipid lowering drug) as this may cause a strong enhancement and prolongation of the effect of NovoNorm; please be sure to inform your doctor if you use gemfibrozil**

Be sure to tell your doctor if:

- You have liver or kidney problems
- You are about to have major surgery or you have recently suffered a severe illness or infection

At such times diabetic control may be lost.
If any of the above applies to you, NovoNorm may not be suitable for you to use. Your doctor will advise you.

Pregnancy
NovoNorm should not be used if you are pregnant or you are planning to become pregnant.

Breast feeding
NovoNorm should not be used if you are breast-feeding.

Driving and using machines
You are advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important if you have reduced or absent awareness of the warning signs of hypoglycaemia or if you have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

7. Can NovoNorm be taken with other medicines?
Your NovoNorm need may change if you take other medicines.

You should tell your doctor, if you take any of these medicines or any other medicines, which you are unsure about:

- Monoamine oxidase inhibitors
- Non-selective beta blocking agents (used to treat high blood pressure and certain heart conditions)
- Angiotensin converting enzyme (ACE)-inhibitors (used to treat certain heart conditions)

- Salicylates (e.g. aspirin)
- Octreotide
- NSAIDS
- Anabolic steroids and corticosteroids
- Oral contraceptives (used for birth control)
- Thiazides
- Danazol
- Thyroid products (used to treat patients with low production of thyroid hormones)
- Sympathomimetics (used to treat asthma)
- Clarithromycin
- **Itraconazole (antifungal drug)**
- **Ketoconazole (antifungal drug)**
- **Gemfibrozil (lipid-lowering drug)**

Your need for NovoNorm may also change if you drink alcohol.