novo nordisk®

NovoNorm®
0.5 mg tablets
1 mg tablets
2 mg tablets

Repaglinide

Qualitative and quantitative composition

NovoNorm® contains repaglinide as the active ingredient. The other ingredients are listed in *List of excipients*.

The 0.5 mg tablet is white, round and convex, engraved with Novo Nordisk logo (Apis bull).
The 1 mg tablet is yellow, round and convex, engraved with Novo Nordisk logo (Apis bull).
The 2 mg tablet is peach-coloured, round and convex, engraved with Novo Nordisk logo (Apis bull).

Pharmacotherapeutic group

Oral anti-diabetic agent.

Manufacturer

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

Therapeutic indications

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 or thiazolidinediones in type 2 diabetes patients who are not satisfactorily controlled on either repaglinide, metformin or thiazolidinediones alone. Treatment should be initiated as an adjunct to diet and exercise to lower the blood glucose in relation to meals.

Posology and method of administration

Repaglinide is given preprandially and is titrated individually to optimise glycaemic control. In addition to self-monitoring by the patient of blood and/or urinary glucose, the patient's blood glucose should be monitored periodically by the physician to determine the minimum effective dose for the patient. Glycosylated haemoglobin levels are also of value in monitoring the patient's response to therapy. Periodic monitoring is necessary to detect inadequate lowering of blood glucose at the recommended maximum level (i.e. primary failure) and to detect loss of adequate blood glucose-lowering response after an initial period of effectiveness (i.e. secondary failure). Short-term administration of repaglinide may be sufficient during periods of transient loss of control in type 2 diabetic patients usually controlled well on diet.
Doses are usually 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 (i.e. preprandially 2, 3, or 4 meals a day). Patients who skip a meal (or add an extra meal) should be instructed to skip (or add) a dose for that meal.
In the case of concomitant use with other active substances, refer to sections *Special warnings and precautions for use* and *Interaction with other medicinal products and other forms of interaction* to assess dosage.

Initial dose
The dose should be determined by the physician, according to the patient's blood glucose response. The recommended starting dose is 0.5 mg per meal in patients naive to all hypoglycaemic agents. One to two weeks should elapse between titration steps (as determined by blood glucose response). If patients are transferred from another oral hypoglycaemic agent the recommended starting dose is 1 mg per meal.

Maintenance
The recommended maximum single dose is 4 mg taken with meals. The total maximum daily dose should not exceed 16 mg.

Patients transferred from other oral hypoglycaemic agents (OHAs)
Patients can be transferred directly from other oral hypoglycaemic agents to repaglinide. However, no exact dose relationship exists between repaglinide and other oral hypoglycaemic agents. The recommended maximum starting dose of patients transferred to repaglinide is 1 mg given before meals.

Combination therapy
Repaglinide can be given in combination with metformin or thiazolidinediones, when blood glucose is insufficiently controlled with metformin, thiazolidinediones or repaglinide alone. The starting dose of repaglinide is the same as for monotherapy. The dose of each drug should be adjusted according to blood glucose response.

Specific patient groups
See *Special warnings and precautions for use*.

Repaglinide is not recommended for use in children below age 18 due to a lack of data on safety and/or efficacy.

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
- Severe hepatic function disorder
- Concomitant use of gemfibrozil (see *Interaction with other medicinal products and other forms of interaction*).

Special warnings and precautions for use

General
Repaglinide should be prescribed if poor blood glucose control and symptoms of diabetes persist despite diet and exercise.
Repaglinide like other insulin secretagogues is capable of producing hypoglycaemia. Combination treatment is associated with an increased risk of hypoglycaemia. When a patient stabilised on any oral hypoglycaemic agent is exposed to stress such as fever, trauma, infection or surgery, a loss of glycaemic control may occur. In such cases, it may be necessary to discontinue repaglinide and treat with insulin on a temporary basis.
The blood glucose-lowering effect of OADs decreases in many patients over time, e.g. due to progression of the severity of the diabetes or to diminished responsiveness to the product. The phenomenon is known as secondary failure, to distinguish it from primary failure, where the drug is ineffective in an individual patient when first given. Adjustment of dose and adherence to diet and exercise should be assessed before classifying a patient as a secondary failure.
No specific clinical studies have been conducted in patients <18 or >75 years of age.
A careful dose titration is recommended in debilitated or malnourished patients. The initial and maintenance dosages should be conservative (see *Posology and method of administration*).

Specific patient groups
Hepatic insufficiency. Patients with impaired liver function may be exposed to higher concentrations of repaglinide and its associated metabolites than would patients with normal liver function receiving usual doses. Therefore, repaglinide should not be used in patients with severe hepatic function disorder (see *Contraindications*) and should be used cautiously in patients with impaired liver function. Longer intervals between dose adjustments should be utilized to allow full assessment of response (see *Pharmacokinetic properties*).
Renal insufficiency. Although there is only weak correlation between repaglinide level and creatinine clearance, the total plasma clearance of the product is decreased in patients with severe renal impairment. As insulin sensitivity is increased in diabetic patients with renal impairment, caution is advised when titrating these patients (see *Pharmacokinetic properties*).

Interaction with other medicinal products and other forms of interaction

As a number of drugs are known to influence glucose repaglinide metabolism, possible interactions should be taken into account by the physician.
In vitro data indicate that repaglinide is metabolised predominantly by CYP2C8 and CYP3A4. Repaglinide appears to be substrate for active hepatic uptake (organic anion transporting protein OATP1B1). Clinical data in healthy volunteers support CYP2C8 as being the most important enzyme involved in repaglinide metabolism with CYP3A4 playing a minor role, but the relative contribution can be increased if CYP2C8 is inhibited. Consequently metabolism, and by that clearance of repaglinide, may be altered by drugs which influence these cytochrome P-450 enzymes via inhibition or induction. Special care should be taken when both inhibitors of CYP2C8 and 3A4 are co-administered simultaneously with repaglinide. Drugs that inhibit OATP1B1 (e.g ciclosporin) may likewise have the potential to increase plasma concentrations of repaglinide.

The following substances may enhance and/or prolong the hypoglycaemic effect of repaglinide: gemfibrozil, trimethoprim, rifampicin, ketoconazole, itraconazole, clarithromycin, ciclosporin, other antidiabetic drugs, monoamine oxidase inhibitors (MAOI), non selective beta blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, NSAIDs, octreotide, alcohol, and anabolic steroids.
A drug interaction study in healthy volunteers showed that co-administration of *gemfibrozil* (600 mg twice daily), an inhibitor of CYP2C8 and OATP1B1, and repaglinide (a single dose of 0.25 mg) increased the repaglinide AUC 8.1-fold and C_{max} 2.4-fold and prolonged the elimination half-life ($t_{½}$) from 1.3 to 3.7 hours resulting in possibly enhanced and prolonged blood glucose-lowering effect of repaglinide. The concomita use of gemfibrozil and repaglinide is contraindicated (see *Contraindicatio*
Co-administration of *trimethoprim* (160 mg twice daily), a weak CYP2C inhibitor, and repaglinide (a single d of 0.25 mg) resulted in slight increas in repaglinide AUC, C_{max} and $t_{½}$ (1.6-fold, 1.4-fold and 1.2-fold respectively) with no statistically significant effects on the blood gluc levels. This lack of pharmacodynami effect was observed with a sub-therapeutic dose of repaglinic Since the safety profile of this combination has not been establish with dosages higher than 0.25 mg f repaglinide and 320 mg for trimethoprim, concomitant use shou be with caution. If concomitant use necessary, careful monitoring of blo glucose and close clinical monitorin should be performed.
Rifampicin, a potent inducer of CYP3A4, but also CYP2C8, acts bot as an inducer and inhibitor of the metabolism of repaglinide. Seven d pre-treatment with rifampicin (600 mg), followed by co-administra of repaglinide (a single dose of 4 m at day seven resulted in a 50% low AUC (effect of a combined inductio and inhibition). When repaglinide w given 24 hours after the last rifamp dose, an 80% reduction of the repaglinide AUC was observed (effect of induction alone).
Concomitant use of rifampicin and repaglinide might therefore induce a need for repaglinide dose adjustm which should be based on carefully monitored blood glucose concentrations at both initiation of rifampicin treatment (acute inhibitic following dosing (mixed inhibition a induction), withdrawal (induction alone) and up to approximately one week after withdrawal of rifampicir where the inductive effect of rifamp is no longer present.
The effect of *ketoconazole*, a proto of potent and competitive inhibitor CYP3A4, on the pharmacokinetics repaglinide has been studied in hea subjects. Co-administration of 200 ketoconazole increased the repaglir (AUC and C_{max}) by 1.2-fold with profiles of blood glucose concentrations altered by less than when administered concomitantly (a single dose of 4 mg repaglinide).
Co-administration of 100 mg *itraconazole*, an inhibitor of CYP3A has also been studied in healthy volunteers, and increased the AUC 1.4-fold. No significant effect on th glucose level in healthy volunteers observed.
In an interaction study in healthy volunteers, co-administration of 250 mg *clarithromycin*, a potent mechanism-based inhibitor of CYP slightly increased the repaglinide (A by 1.4-fold and C_{max} by 1.7-fold ar increased the mean incremental AU of serum insulin by 1.5-fold and th maximum concentration by 1.6-fol The exact mechanism of this interaction is not clear.
Ciclosporin (100 mg), an inhibitor c CYP3A4 and a strong OATP1B1 inhibitor, increased the repaglinide (0.25 mg) C_{max} 1.8-fold and the AU 2.5-fold in an interaction study wit healthy volunteers.
β-blocking agents may mask the symptoms of hypoglycaemia.
Co-administration of *cimetidine, nifedipine, oestrogen* or *simvastati* with repaglinide, all CYP3A4 substrates, did not significantly alte the pharmacokinetic parameters o repaglinide.
Repaglinide had no clinically releva effect on the pharmacokinetic properties of *digoxin, theophylline*

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, rifampicin, barbiturates, carbamazepine, thiazides, corticosteroids, danazol, thyroid hormones* and *sympathomimetics*. Concomitant *oral contraceptive* administration *(ethinylestradiol/levonorgestrel)* did not alter repaglinide's total bioavailabilty to a clinically relevant degree, although peak levels of repaglinide occurred earlier. Repaglinide had no clinically meaningful effect upon bioavailability of levonorgestrel, but effects on ethinylestradiol bioavailability cannot be excluded.When the above medications are administered to or withdrawn from a patient receiving repaglinide, the patient should be observed closely for changes in glycaemic control.

Pregnancy and lactation

No studies of repaglinide in pregnant or lactating women have been performed. Therefore the safety of repaglinide in pregnant women cannot be assessed. Repaglinide was not teratogenic in animal studies. Nonteratogenic abnormal limb development in foetuses and newborn pups was observed in rats exposed to high doses in the last stage of pregnancy and during the lactation period. Repaglinide has been detected in the milk of experimental animals.

Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

Undesirable effects

General

The most frequently reported Adverse Drug Reactions (ADR) are change in blood glucose level, i.e. hypoglycaemia. The occurrence of such reactions depends, as for every diabetes therapy, on individual factors, such as dietary habits, dosage, exercise and stress. Based on the experience with repaglinide and with other hypoglycaemic agents the following ADRs have been seen. Frequencies are defined as: Common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated form the available data).

Immune system disorders

Very rare: Allergy
Generalised hypersensitivity reactions (e.g. anaphylactic reaction), or immunological reactions such as vasculitis.

Metabolism and nutrition disorders

Common: Hypoglycaemia
Not known: Hypoglycaemic coma and hypoglycaemic unconsciousness
As with other antidiabetic agents, hypoglycaemia has been observed after administration of repaglinide. The symptoms may include anxious feeling, dizziness, sweating, tremor, hunger and difficulty in concentration. These reactions are mostly mild and can be treated by intake of carbohydrates. If severe and requiring third party assistance, infusion of glucose may be necessary. Interactions with other medicinal products may increase the risk of hypoglycaemia (see *Interaction with other medicinal products and other forms of interaction*).

Eye disorders

Very rare: Visual disturbance
Changes in blood glucose levels may result in blurred vision and visual disturbances, especially at the initiation of treatment with hypoglycaemic agents. These changes are usually transient.

Cardiac disorders

Rare: Cardiovascular disease
Type 2 diabetes is associated with an increased risk for cardiovascular disease. One epidemiological study suggested an increased risk of acute coronary syndrome in repaglinide treated patients as compared to sulphonylurea treated patients, but not as compared to metformin or acarbose treated patients. However, a causal relationship was not established.

Gastro-intestinal disorders

Common: Abdominal pain, diarrhoea
Very rare: Vomiting and constipation
Not known: Nausea
Gastro-intestinal complaints such as abdominal pain, diarrhoea, nausea, vomiting and constipation have been reported in clinical trials. The rate and severity of these symptoms did not differ from that seen with other oral insulin secretagogues.

Hepatobiliary disorders

Very rare: Hepatic function abnormal
In very rare cases, severe hepatic dysfunction has been reported. However, a causal relationship with repaglinide has not been established.

Very rare: Hepatic enzymes increased
Most of the reported cases were mild and transient, and very few patients discontinued treatment due to increase in liver enzymes.

Skin and subcutaneous tissue disorders

Not known: Hypersensitivity
Hypersensitivity reactions may occur as erythema, itching, rashes and urticaria.

Overdose

In a clinical trial in patients with type 2 diabetes repaglinide was given as weekly escalating doses from 4-20 mg with each of four meals daily over a 6 week period. Few adverse events were seen other than those associated with the intended effect of lowering blood glucose. As hypoglycaemia in this study was avoided through increased calorie intake, a relative overdose may result in an exaggerated glucose lowering effect with development of hypoglycaemic symptoms (dizziness, sweating, tremor, headache etc.). Should these symptoms occur, adequate action should be taken to correct the low blood glucose (oral carbohydrates). More severe hypoglycaemia with seizure, loss of consciousness or coma should be treated with IV glucose.

Pharmacodynamic properties

Repaglinide is a short-acting insulin secretagogue. Repaglinide lowers the blood glucose levels acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning β-cells in the pancreatic islets. Repaglinide closes the ATP-dependent potassium channels in the β-cell membrane by binding to sites on the β-cell. This depolarises the β-cell and leads to an opening of the calcium channels. The resulting increased calcium influx induces insulin secretion from the β-cell.
In type 2 diabetic patients, the insulinotropic response to a meal occurred within 30 minutes after an oral dose of repaglinide. This resulted in a blood glucose-lowering effect throughout the meal period. Plasma repaglinide levels decreased rapidly, and low drug concentrations were seen in the plasma of type 2 diabetic patients 4 hours post administration. A dose dependent decrease in blood glucose was demonstrated in type 2 diabetic patients when administered in doses from 0.5 to 4 mg repaglinide. Clinical study results have shown that repaglinide should be dosed prior to meals (preprandial dosing). Doses are usually 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.

Pharmacokinetic properties

Repaglinide is rapidly absorbed from the gastrointestinal tract, which leads to a rapid increase in the plasma concentration of the drug. The peak plasma levels occur within one hour post administration. After reaching a maximum, the plasma level decreases rapidly, and repaglinide is eliminated within 4-6 hours. The plasma elimination half life is approximately one hour. Repaglinide pharmacokinetics is characterised by a mean absolute bioavailability of 63% (CV 11%) low volume of distribution, 30 L (consistent with distribution into intracellular fluid), and rapid elimination from the blood. A high interindividual variability (60%) in repaglinide plasma concentrations has been detected in clinical trials. Intraindividual variability is low to moderate (35%) and as repaglinide should be titrated against the clinical response, efficacy is not affected by interindividual variability.

Renal insufficiency:
Single-dose and steady-state pharmacokinetics of repaglinide were evaluated in patients with type 2 diabetes and various degrees of renal impairment. Both AUC and C_{max} of repaglinide were the same in patients with normal and mild to moderately impaired renal function (mean values 56.7 ng/mL*hr vs 57.2 ng/mL*hr and 37.5 ng/mL vs 37.7 ng/mL, respectively). Patients with severely reduced renal function had somewhat elevated mean AUC and C_{max} values (98.0 ng/mL*hr and 50.7 ng/mL, respectively), but this study showed only a weak correlation between repaglinide levels and creatinine clearance. Initial dose adjustment does not appear to be necessary for patients with renal dysfunction. Subsequent increases in repaglinide should be made carefully in patients with type 2 diabetes who have severe renal function impairment or renal failure requiring hemodialysis.

Hepatic insufficiency:
A single-dose, open-label study was conducted in 12 healthy subjects and 12 patients with chronic liver disease (CLD) classified by Child-Pugh Scale and caffeine clearance. Patients with moderate to severe impairment of liver function had higher and more prolonged serum concentrations of both total and unbound repaglinide than healthy subjects ($AUC_{healthy}$: 91.6 ng/mL*hr; $AUC_{CLD\ patients}$: 368.9 ng/mL*hr; $C_{max,\ healthy}$: 46.7 ng/mL; $C_{max,\ CLD\ patients}$: 105.4 ng/mL). AUC was statistically correlated with caffeine clearance. No difference in glucose profiles was observed across patient groups.

Patients with impaired liver functio may be exposed to higher concentrations of repaglinide and i associated metabolites than would patients with normal liver function receiving usual doses. Therefore, repaglinide should not be used in patients with severe hepatic functi disorder and be used cautiously in patients with impaired liver functio Longer intervals between dose adjustments should be utilized to a full assessment of response.

Repaglinide is highly bound (greater than 98%) to plasma prot in humans.
No clinically relevant differences w seen in the pharmacokinetics of repaglinide, when repaglinide was administered 0, 15 or 30 minutes before a meal or in a fasting state. Repaglinide is completely metaboli predominantly via CYP2C8 but alsc CYP3A4, and no metabolites with clinically relevant hypoglycaemic ef have been identified. Repaglinide a its metabolites are excreted primari via the bile. A small fraction (approximately 8%) of the administered dose appears in the u preliminary as metabolites. Less tha 2% of the parent drug is recovered faeces.

Preclinical safety data

Preclinical safety data revealed no special hazard for humans based o conventional studies of safety pharmacology, repeated dose toxic genotoxicity and carcinogenic potential.

List of excipients

Cellulose, microcrystalline (E460); calcium hydrogen phosphate, anhydrous; maize starch; polacrilin potassium; povidone K25; glycerol; magnesium stearate; meglumine; poloxamer 188; iron oxides (E172) yellow and red for 1 and 2 mg tablets, respectively.

Presentations

Three strengths of tablets are available. The strengths are 0.5 mg (white tablets), 1 mg (yellow tablets) and 2 mg (peach-coloured tablets).
The blister pack (aluminium /alumini contains 30, 90 or 120 tablets.

Special precautions for storage

Store in a dry place at 15°C - 25°C order to protect from moisture. Store in the original package. Keep of the reach and sight of children. D not use after the expiry date printe the package.