# 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*.

NovoNorm® tablets are round and convex, engraved with Novo Nordisk logo (Apis bull).
0.5 mg tablet: white
1 mg tablet: yellow
2 mg tablet: peach-coloured

**Therapeutic indications**
Repaglinide is indicated in adults with type 2 diabetes mellitus whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. Repaglinide is also indicated in combination with metformin in adults with type 2 diabetes mellitus who are not satisfactorily controlled on metformin 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**
**Posology**
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 dose 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.

*Initial dose*
The dosage should be determined by the physician, according to the patient's requirements. The recommended starting dose is 0.5 mg. 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.

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

*Special populations*
*Elderly*
No clinical trials have been conducted in patients > 75 years of age.

*Renal impairment*
Repaglinide is not affected by renal disorders.
Eight percent of one dose of repaglinide is excreted through the kidneys and total plasma clearance of the product is decreased in patients with renal impairment. As insulin sensitivity is increased in diabetic patients with renal impairment, caution is advised when titrating these patients.

*Hepatic impairment*
No clinical studies have been conducted in patients with 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*).

*Debilitated or malnourished patients*
In debilitated or malnourished patients, the initial and maintenance dosage should be conservative and careful dose titration is required to avoid hypoglycaemic reactions.

*Patients receiving other oral hypoglycaemic medicinal products*
Patients can be transferred directly from other oral hypoglycaemic medicinal products to repaglinide. However, no exact dosage relationship exists between repaglinide and other oral hypoglycaemic medicinal products. The recommended maximum starting dose of patients transferred to repaglinide is 1 mg given before main meals.

Repaglinide can be given in combination with metformin when the blood glucose is insufficiently controlled with metformin alone. The dosage of metformin should be maintained and repaglinide administered concomitantly. The starting dose of repaglinide is 0.5 mg. Titration is according to blood glucose response.

*Paediatric population*
The safety and efficacy of repaglinide in children below 18 years have not been established. No data are available.

**Method of administration**
Doses are taken orally usually 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, refer to sections *Special warnings and precautions for use* and *Interaction with other medicinal products and other forms of interaction* to assess dosage.

**Contraindications**
- Hypersensitivity to repaglinide or any of the excipients in NovoNorm®
- Diabetes mellitus type 1, 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, exercise and weight reduction.

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.

*Hypoglycaemia*
Repaglinide, like other insulin secretagogues, is capable of producing hypoglycaemia.

*Combination with insulin secretatgogues*
The blood glucose-lowering effect of OADs decreases in many patients over time. This may be due to progression of the severity of the diabetes or to diminished responsiveness to the product. This phenomenon is known as secondary failure, to distinguish it from primary failure, where the product 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.
Repaglinide acts through a distinct binding site with a short action on the β-cells. Use of repaglinide in case of secondary failure to insulin secretagogues has not been investigated in clinical trials. Trials investigating the combination with other insulin secretagogues have not been performed.

*Combination with Neutral Protamine Hagedorn (NPH) insulin or thiazolidinediones*
Trials of combination therapy with NPH insulin or thiazolidinediones have been performed. However, the benefit risk profile remains to be established when comparing to other combination therapies.

*Combination with metformin*
Combination treatment with metformin is associated with an increased risk of hypoglycaemia.

*Concomitant use*
Repaglinide should be used with caution or be avoided in patients receiving medicinal products which influence repaglinide metabolism (see section *Interaction with other medicinal products and other forms of interaction*). If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed.

*Acute coronary syndrome*
The use of repaglinide might be associated with an increased incidence of acute coronary syndrome (e.g. myocardial infarction).

**Interaction with other medicinal products and other forms of interaction**
A number of substances are known to influence the clearance of repaglinide. Possible interactions should be taken into account by the physician.
*In vitro* data indicate that repaglinide is metabolised predominantly by CYP2C8 , but also by CYP3A4.
Clinical data in healthy volunteers support 2C8 as being the most important enzyme involved in repaglinide metabolism with 3A4 playing a minor role, but the relative contribution of 3A4 can be increased if 2C8 is inhibited. Consequently metabolism, and by that clearance of repaglinide, may be altered by substances which influence these cytochrome P-450 enzymes via inhibition or induction. Special care should be taken when inhibitors of both 2C8 and 3A4 are co-administered simultaneously with repaglinide.
Based on *in vitro* data, repaglinide appears to be a substrate for active hepatic uptake (organic anion transporting protein OATP1B1). Substances that inhibit OATP1B1 may likewise have the potential to increase plasma concentrations of repaglinide, as has been shown for ciclosporin (see below).
The following substances may enhance and/or prolong the hypoglycaemic effect of repaglinide: Gemfibrozil, trimethoprim, rifampicin, ketoconazole, itraconazole, clarithromycin, ciclosporin, deferasirox, clopidogrel, other antidiabetic substances, monoamine oxidase inhibitors (MAOI), non-selective beta-blocking substances, angiotensin converting enzyme (ACE)-inhibitors, salicylates, NSAIDs, octreotide, alcohol, and anabolic steroids.
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 in healthy volunteers. Half-life was prolonged from 1.3 hr to 3.7 hr, resulting in possibly enhanced and prolonged blood glucose-lowering effect of repaglinide, and plasma repaglinide concentration at 7 hr was increased 28.6-fold by gemfibrozil. The concomitant use of gemfibrozil and repaglinide is contraindicated (see *Contraindications*).
There is no drug-drug interaction between *fenofibrate* and repaglinide.
Co-administration of *trimethoprim* (160 mg twice daily), a moderate CYP2C8 inhibitor, and repaglinide (a single dose of 0.25 mg) increased the 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 glucose levels. This lack of pharmacodynamic effect was observed with a sub-therapeutic dose of repaglinide. Since the safety profile of this combination has not been established with dosages

higher than 0.25 mg for repaglinide and 320 mg for trimethoprim, concomitant use should be avoided. If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed.
*Rifampicin*, a potent inducer of CYP3A4, but also CYP2C8, acts both as an inducer and inhibitor of the metabolism of repaglinide. Seven days pre-treatment with rifampicin (600 mg), followed by co-administration of repaglinide (a single dose of 4 mg) at day seven resulted in a 50% lower AUC (effect of a combined induction and inhibition). When repaglinide was given 24 hours after the last rifampicin 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 adjustment which should be based on carefully monitored blood glucose concentrations at both initiation of rifampicin treatment (acute inhibition), following dosing (mixed inhibition and induction), withdrawal (induction alone) and up to approximately one week after withdrawal of rifampicin where the inductive effect of rifampicin is no longer present.
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 and $C_{max}$) by 1.2-fold with profiles of blood glucose concentrations altered by less than 8% when administered concomitantly (a single dose of 4 mg repaglinide).
Co-administration of 100 mg *itraconazole*, an inhibitor of CYP3A4, has also been studied in healthy volunteers, and increased the AUC by 1.4-fold. No significant effect on the glucose level in healthy volunteers was observed.
Co-administration of 250 mg *clarithromycin*, a potent mechanism-based inhibitor of CYP3A4, to healthy volunteers slightly increased the repaglinide (AUC) by 1.4-fold and $C_{max}$ by 1.7-fold and increased the mean incremental AUC of serum insulin by 1.5-fold and the maximum concentration by 1.6-fold. The exact mechanism of this interaction is not clear.
Concomitant administration of a repeated dose at 100 mg *ciclosporin*, an inhibitor of CYP3A4 and OATP1B1, and repaglinide at a single dose of 0.25 mg to healthy volunteers increased repaglinide AUC and $C_{max}$ about 2.5-fold and 1.8-fold respectively. Since the interaction has not been established with dosages higher than 0.25mg for repaglinide, the concomitant use of ciclosporin with repaglinide should be avoided. If the combination is necessary, careful clinical and blood glucose monitoring should be performed (see *Special warnings and precautions for use*).
Co-administration of *deferasirox* (30 mg/kg/day, 4 days), a moderate inhibitor of CYP2C8 and CYP3A4, and repaglinide (single dose, 0.5 mg) in healthy volunteers increased repaglinide exposure (AUC) 2.3-fold (90% CI [2.03-2.63]) and $C_{max}$ 1.6-fold (90% CI [1.42-1.84]) and resulted in a small, significant decrease in blood glucose. Since the interaction has not been established with dosages higher than 0.5 mg for repaglinide, the concomitant use of deferasirox with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed (see *Special warnings and precautions for use*).
Co-administration of *clopidogrel* (300mg loading dose), a CYP2C8 inhibitor, increased repaglinide exposure ($AUC_{0-\infty}$) 5.1-fold and continued administration (75mg daily dose) increased repaglinide exposure ($AUC_{0-\infty}$) 3.9-fold. A small, significant decrease in blood glucose values was observed. If repaglinide and clopidogrel are used concomitantly, careful clinical and blood glucose monitoring should be performed (see *Special warnings and precautions for use*).
β-blocking agents may mask the symptoms of hypoglycaemia.

Co-administration of *cimetidine, nifedipine, oestrogen* or *simvastatin* with repaglinide, all CYP3A4 substrates, did not significantly alter the pharmacokinetic parameters of repaglinide.
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, rifampicin, barbiturates, carbamazepine, 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.

*Paediatric population*
No interaction studies have been performed in children and adolescents.

**Fertility, pregnancy and lactation**
No studies of repaglinide in pregnant or breast-feeding women have been performed. Therefore the safety of repaglinide in pregnant and breast-feeding women cannot be assessed. Non-teratogenic abnormal limb development has been observed in animal and repaglinide has been detected in the milk of animals (see *Preclinical safety data*). For that reason repaglinide should be avoided during pregnancy and should not be used in lactating women.

**Effects on ability to drive and use machines**
NovoNorm® has no direct influence on the ability to drive and use machines but may cause hypoglycaemia.
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**
*Summary of the safety profile*
The most frequently reported adverse reactions are changes in blood glucose levels, i.e. hypoglycaemia. The occurrence of such reactions depends on individual factors, such as dietary habits, dosage, exercise and stress.

*Tabulated list of adverse reactions*
Based on the experience with repaglinide and with other hypoglycaemic agents the following adverse reactions 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 from the available data).

**Immune system disorders**
Very rare: Allergic reactions*

**Metabolism and nutrition disorders**
Common: Hypoglycaemia
Not known: Hypoglycaemic coma and hypoglycaemic unconsciousness

**Eye disorders**
Very rare: Refraction disorder*

**Cardiac disorders**
Rare: Cardiovascular disease*

**Gastro-intestinal disorders**
Common: Abdominal pain, diarrhoea
Very rare: Vomiting and constipation
Not known: Nausea

**Hepatobiliary disorders**
Very rare: Abnormal hepatic function, increased liver enzymes*

**Skin and subcutaneous tissue disorders**
Not known: Hypersensitivity*

* see section *Description of selected adverse reactions* below

*Description of selected adverse reactions*
*Allergic reactions*
Generalised hypersensitivity reactions (e.g. anaphylactic reaction), or immunological reactions such as vasculitis.

*Refraction disorders*
Changes in blood glucose levels have been known to result in transient visual disturbances, especially at the initiation of treatment.

*Cardiac disorders*
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.

*Abnormal hepatic function, increased liver enzymes*
Isolated cases of increased liver enzymes have been reported during treatment with repaglinide. Most cases were mild and transient, and very few patients discontinued treatment due to increased liver enzymes. In very rare cases, severe hepatic dysfunction has been reported.

*Hypersensitivity*
Hypersensitivity reactions may occur as erythema, itching, rashes and urticaria. There is no reason to suspect cross-allergenicity with sulfonylurea due to the difference in chemical structure.

**Overdose**
Repaglinide has been given with weekly escalating doses from 4-20 mg four times daily in a 6 week period. No safety concerns were raised. 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 intravenous glucose.

**Pharmacodynamic properties**
*Mechanism of action*
Repaglinide is a short-acting oral 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 ATP-dependent potassium channels in the β-cell membrane via a target protein different from other secretagogues. 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.

*Pharmacodynamic effects*
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. The elevated insulin levels did not persist beyond the time of the meal challenge. Plasma repaglinide levels decreased rapidly, and low concentrations were seen in the plasma of type 2 diabetic patients 4 hours post-administration.

*Clinical efficacy and safety*
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 is optimally dosed in relation to main meals (preprandial dosing). Doses are usually taken within 15 minutes of the meal, but the time may vary from immediately preceding the meal to as long as 30 minutes before the meal.

**Pharmacokinetic properties**
*Absorption*
Repaglinide is rapidly absorbed from the gastrointestinal tract, which leads to a rapid increase in the plasma concentration of the substance. The peak plasma level occurs within one hour post administration. After reaching a maximum, the plasma level decreases rapidly.
Repaglinide pharmacokinetics are characterised by a mean absolute bioavailability of 63% (CV 11%). No clinically relevant differences were seen in the pharmacokinetics of repaglinide, when repaglinide was administered 0, 15 or 30 minutes before a meal or in fasting state. 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.

*Distribution*
Repaglinide pharmacokinetics are characterised by low volume of distribution, 30 L (consistent with distribution into intracellular fluid), and is highly bound to plasma proteins in humans (greater than 98%).

*Elimination*
Repaglinide is eliminated rapidly within 4-6 hours from the blood. The plasma elimination half-life is approximately one hour.
Repaglinide is almost completely metabolised, and no metabolites with clinically relevant hypoglycaemic effect have been identified. Repaglinide metabolites are excreted primarily via the bile. A small fraction (less than 8%) of the administered dose appears in the urine, primarily as metabolites. Less than 2% of repaglinide is recovered in faeces.

*Special patient groups*
Repaglinide exposure is increased in patients with hepatic insufficiency and in the elderly type 2 diabetic patients. The AUC (SD) after 2 mg single dose exposure (4mg in patients with hepatic insufficiency) was 31.4 ng/ml x hr (28.3) in healthy volunteers, 304.9 ng/ml x hr (228.0) in patients with hepatic insufficiency, and 117.9 ng/ml x hr (83.8) in the elderly type 2 diabetic patients.
After a 5 day treatment of repaglinide (2 mg x 3/day) in patients with a severe impaired renal function (creatinine clearance: 20-39 ml/min), the results showed a significant 2-fold increase of the exposure (AUC) and half-life ($t_{1/2}$) as compared to patients with normal renal function.

*Paediatric population*
No data available.

**Preclinical safety data**
Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
Repaglinide was not teratogenic in animal studies. Embryotoxicity, abnormal limb development in rat foetuses and newborn pups, was observed in female rats exposed to high doses in the last stage of pregnancy and during the lactation period. Repaglinide was detected in the milk of animals.

**List of excipients**
Cellulose, microcrystalline (E460); calcium hydrogen phosphate, anhydrous; maize starch; polacrilin potassium; povidone (K25); glycerol 85 %; magnesium stearate; meglumine; poloxamer 188; iron oxides yellow and red for 1 and 2 mg tablets, respectively.

**Presentations**
The blister pack (aluminium /aluminium) contains 90 tablets.

**Special precautions for storage**
Store in the original package at 15°C - 25°C to protect from moisture.
Keep out of the sight and reach of children. Do not use after the expiry date printed on the package.

**Manufacturer**
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