ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NovoNorm 0.5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg of repaglinide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Repaglinide tablets are white, round and convex and engraved with Novo Nordisk logo (Apis bull).

4. CLINICAL PARTICULARS

4.1 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.

4.2 Posology and method of administration

Posology

Repaglinide is given preprandially and is titrated individually to optimise glycaemic control. In addition to the usual self-monitoring by the patient of blood and/or urinary glucose, the patient's blood glucose must 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 medicinal product, 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 studies have been conducted in patients >75 years of age.

Renal impairment
Repaglinide is not affected by renal disorders (see section 5.2).
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.

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 the 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. In this case, the dosage of metformin should be maintained and repaglinide administered concomitantly. The starting dose of repaglinide is 0.5 mg, taken before main meals; titration is according to blood glucose response as for monotherapy.

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

Method of administration

Repaglinide should be taken before main meals (i.e. preprandially).

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 4.4 and 4.5 to assess the dosage.

4.3 Contraindications

- Hypersensitivity to repaglinide or to any of the excipients listed in section 6.1.
- Diabetes mellitus type 1, C-peptide negative.
- Diabetic ketoacidosis, with or without coma.
- Severe hepatic function disorder.
- Concomitant use of gemfibrozil (see section 4.5).

4.4 Special warnings and precautions for use

General

Repaglinide should only be prescribed if poor blood glucose control and symptoms of diabetes persist despite adequate attempts at dieting, exercise and weight reduction.

When a patient stabilised on any oral hypoglycaemic medicinal product is exposed to stress such as fever, trauma, infection or surgery, a loss of glycaemic control may occur. At such times, 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 secretagogues

The blood glucose-lowering effect of oral hypoglycaemic medicinal products decreases in many patients over time. This may be due to progression of the severity of the diabetes or to diminished responsiveness to the medicinal product. This phenomenon is known as secondary failure, to distinguish it from primary failure, where the medicinal 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.

Acute coronary syndrome

The use of repaglinide might be associated with an increased incidence of acute coronary syndrome (e.g. myocardial infarction), see sections 4.8 and 5.1.

Concomitant use

Repaglinide should be used with caution or be avoided in patients receiving medicinal products which influence repaglinide metabolism (see section 4.5). If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products are known to influence repaglinide metabolism. Possible interactions should therefore 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 CYP2C8 as being the most important enzyme involved in repaglinide metabolism with CYP3A4 playing a minor role, but the relative contribution of CYP3A4 can be increased if CYP2C8 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 CYP2C8 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, clarithromycin, itraconazole, ketokonazole, trimethoprim, 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 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 section 4.3).

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, the concomitant use of trimethoprim with repaglinide should be avoided. If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed (see section 4.4).

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 two weeks after withdrawal of rifampicin where the inductive effect of rifampicin is no longer present. It cannot be excluded that other inducers, e.g. phenytoin, carbamazepine, phenobarbital, St John's wort, may have a similar effect.

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. In an interaction study in healthy volunteers, co-administration of 250 mg clarithromycin, a potent mechanism-based inhibitor of CYP3A4, 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.

In a study conducted in healthy volunteers, the concomitant administration of repaglinide (a single

dose of 0.25 mg) and ciclosporin (repeated dose at 100 mg) 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 0.25 mg for repaglinide, the concomitant use of ciclosporin with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed (see section 4.4).

In an interaction study with healthy volunteers, co-administration of deferasirox (30 mg/kg/day, 4 days), a moderate inhibitor of CYP2C8 and CYP3A4, and repaglinide (single dose, 0.5 mg) resulted in an increase in repaglinide systemic exposure (AUC) to 2.3-fold (90% CI [2.03-2.63]) of control, a 1.6-fold (90% CI [1.42-1.84]) increase in C_{max}, and a small, significant decrease in blood glucose values. 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 section 4.4).

In an interaction study with healthy volunteers, co-administration of *clopidogrel* (300 mg loading dose), a CYP2C8 inhibitor, increased repaglinide exposure (AUC0–∞) 5.1-fold and continued administration (75 mg daily dose) increased repaglinide exposure (AUC0–∞) 3.9-fold. A small, significant decrease in blood glucose values was observed. Since the safety profile of the co-treatment has not been established in these patients, the concomitant use of clopidogrel and repaglinide should be avoided. If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed (see section 4.4).

β-blocking medicinal products 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.

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

Paediatric population

No interaction studies have been performed in children and adolescents.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no studies of repaglinide in pregnant women. Repaglinide should be avoided during pregnancy.

Breast-feeding

There are no studies in breast-feeding women. Repaglinide should not be used in breast-feeding women.

Fertility

Data from animal studies investigating effects on embryofetal and offspring development as well as excretion in milk is described in section 5.3.

4.7 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 whilst 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.

4.8 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 medicinal products 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) and not known (cannot be estimated from the available data).

Immune system disorders	Allergic reactions*	Very rare
Metabolism and nutrition disorders	Hypoglycaemia	Common
	Hypoglycaemic coma and hypoglycaemic unconsciousness	Not known
Eye disorders	Refraction disorder*	Very rare
Cardiac disorders	Cardiovascular disease	Rare
Gastrointestinal disorders	Abdominal pain, diarrhoea	Common
	Vomiting, constipation	Very rare
	Nausea	Not known
Hepatobiliary disorders	Abnormal hepatic function, increased liver enzymes*	Very rare
Skin and subcutaneous tissue disorders	Hypersensitivity*	Not known

* 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 commencement of treatment. Such disturbances have only been reported in very few cases after initiation of repaglinide treatment. No such cases have led to discontinuation of repaglinide treatment in clinical trials.

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 of the skin may occur as erythema, itching, rashes and urticaria. There is no reason to suspect cross-allergenicity with sulphonylurea due to the difference in chemical structure.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Drugs used in diabetes, other blood glucose lowering drugs, excl. insulins, ATC code: A10BX02

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.

One epidemiological study suggested an increased risk of acute coronary syndrome in repaglinide treated patients as compared to sulfonylurea treated patients (see sections 4.4 and 4.8).

5.2 Pharmacokinetic properties

Absorption

Repaglinide is rapidly absorbed from the gastrointestinal tract, which leads to a rapid increase in the plasma concentration of the active 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 the 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 1% 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 (4 mg 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 are available.

5.3 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 shown not to be teratogenic in animal studies. Embryotoxicity, abnormal limb development in rat foetuses and new born 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)
Calcium hydrogen phosphate, anhydrous
Maize starch
Polacrilin potassium
Povidone (polyvidone)
Glycerol 85%
Magnesium stearate
Meglumine
Poloxamer

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

The blister pack (aluminium/aluminium) contains 30, 90, 120 or 270 tablets, respectively.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/98/076/004-006, EU/1/98/076/023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 August 1998
Date of last renewal: 23 July 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

NovoNorm 1 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg of repaglinide.

For the full list of excipients, see section 6.1.

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Initial dose

The dosage should be determined by the physician, according to the patient's requirements.
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The total maximum daily dose should not exceed 16 mg.

Special populations

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Renal impairment
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Hepatic impairment
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Combination with Neutral Protamine Hagedorn (NPH) insulin or thiazolidinediones

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Combination with metformin

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Acute coronary syndrome

The use of repaglinide might be associated with an increased incidence of acute coronary syndrome (e.g. myocardial infarction), see sections 4.8 and 5.1.

Concomitant use

Repaglinide should be used with caution or be avoided in patients receiving medicinal products which influence repaglinide metabolism (see section 4.5). If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed.

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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 two weeks after withdrawal of rifampicin where the inductive effect of rifampicin is no longer present. It cannot be excluded that other inducers, e.g. phenytoin, carbamazepine, phenobarbital, St John's wort, may have a similar effect.

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. In an interaction study in healthy volunteers, co-administration of 250 mg clarithromycin, a potent mechanism-based inhibitor of CYP3A4, 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.

In a study conducted in healthy volunteers, the concomitant administration of repaglinide (a single dose of 0.25 mg) and ciclosporin (repeated dose at 100 mg) 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 0.25 mg for repaglinide, the concomitant use of ciclosporin with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed (see section 4.4).

In an interaction study with healthy volunteers, co-administration of deferasirox (30 mg/kg/day, 4 days), a moderate inhibitor of CYP2C8 and CYP3A4, and repaglinide (single dose, 0.5 mg) resulted in an increase in repaglinide systemic exposure (AUC) to 2.3-fold (90% CI [2.03-2.63]) of control, a 1.6-fold (90% CI [1.42-1.84]) increase in C_{max}, and a small, significant decrease in blood glucose values. 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 section 4.4).

In an interaction study with healthy volunteers, co-administration of *clopidogrel* (300 mg loading dose), a CYP2C8 inhibitor, increased repaglinide exposure (AUC0–∞) 5.1-fold and continued administration (75 mg daily dose) increased repaglinide exposure (AUC0–∞) 3.9-fold. A small, significant decrease in blood glucose values was observed. Since the safety profile of the co-treatment has not been established in these patients, the concomitant use of clopidogrel and repaglinide should be avoided. If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed (see section 4.4).

β-blocking medicinal products 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.

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

Paediatric population

No interaction studies have been performed in children and adolescents.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no studies of repaglinide in pregnant women. Repaglinide should be avoided during pregnancy.

Breast-feeding

There are no studies in breast-feeding women. Repaglinide should not be used in breast-feeding women.

Fertility

Data from animal studies investigating effects on embryofetal and offspring development as well as excretion in milk is described in section 5.3.

4.7 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 whilst 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.

4.8 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 medicinal products 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) and not known (cannot be estimated from the available data).

Immune system disorders	Allergic reactions*	Very rare
Metabolism and nutrition disorders	Hypoglycaemia	Common
	Hypoglycaemic coma and hypoglycaemic unconsciousness	Not known
Eye disorders	Refraction disorder*	Very rare
Cardiac disorders	Cardiovascular disease	Rare
Gastrointestinal disorders	Abdominal pain, diarrhoea	Common
	Vomiting, constipation	Very rare
	Nausea	Not known
Hepatobiliary disorders	Abnormal hepatic function, increased liver enzymes*	Very rare
Skin and subcutaneous tissue disorders	Hypersensitivity*	Not known

* 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 commencement of treatment. Such disturbances have only been reported in very few cases after initiation of repaglinide treatment. No such cases have led to discontinuation of repaglinide treatment in clinical trials.

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 of the skin may occur as erythema, itching, rashes and urticaria. There is no reason to suspect cross-allergenicity with sulphonylurea due to the difference in chemical structure.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Drugs used in diabetes, other blood glucose lowering drugs, excl. insulins, ATC code: A10BX02

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.

One epidemiological study suggested an increased risk of acute coronary syndrome in repaglinide treated patients as compared to sulfonylurea treated patients (see sections 4.4 and 4.8).

5.2 Pharmacokinetic properties

Absorption

Repaglinide is rapidly absorbed from the gastrointestinal tract, which leads to a rapid increase in the plasma concentration of the active 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 the 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 1% 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 (4 mg 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 are available.

5.3 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 shown not to be teratogenic in animal studies. Embryotoxicity, abnormal limb development in rat foetuses and new born 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)
Calcium hydrogen phosphate, anhydrous
Maize starch
Polacrilin potassium
Povidone (polyvidone)
Glycerol 85%
Magnesium stearate
Meglumine
Poloxamer
Iron oxide, yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

The blister pack (aluminium/aluminium) contains 30, 90, 120 or 270 tablets, respectively.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/98/076/011-013, EU/1/98/076/024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 August 1998
Date of last renewal: 23 July 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

NovoNorm 2 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of repaglinide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Repaglinide tablets are peach-coloured, round and convex and engraved with Novo Nordisk logo (Apis bull).

4. CLINICAL PARTICULARS

4.1 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.

4.2 Posology and method of administration

Posology

Repaglinide is given preprandially and is titrated individually to optimise glycaemic control. In addition to the usual self-monitoring by the patient of blood and/or urinary glucose, the patient's blood glucose must 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 medicinal product, 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 studies have been conducted in patients >75 years of age.

Renal impairment
Repaglinide is not affected by renal disorders (see section 5.2).
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.

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 the 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. In this case, the dosage of metformin should be maintained and repaglinide administered concomitantly. The starting dose of repaglinide is 0.5 mg, taken before main meals; titration is according to blood glucose response as for monotherapy.

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

Method of administration

Repaglinide should be taken before main meals (i.e. preprandially).

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 4.4 and 4.5 to assess the dosage.

4.3 Contraindications

- Hypersensitivity to repaglinide or to any of the excipients listed in section 6.1.
- Diabetes mellitus type 1, C-peptide negative.
- Diabetic ketoacidosis, with or without coma.
- Severe hepatic function disorder.
- Concomitant use of gemfibrozil (see section 4.5).

4.4 Special warnings and precautions for use

General

Repaglinide should only be prescribed if poor blood glucose control and symptoms of diabetes persist despite adequate attempts at dieting, exercise and weight reduction.

When a patient stabilised on any oral hypoglycaemic medicinal product is exposed to stress such as fever, trauma, infection or surgery, a loss of glycaemic control may occur. At such times, 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 secretagogues

The blood glucose-lowering effect of oral hypoglycaemic medicinal products decreases in many patients over time. This may be due to progression of the severity of the diabetes or to diminished responsiveness to the medicinal product. This phenomenon is known as secondary failure, to distinguish it from primary failure, where the medicinal 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.

Acute coronary syndrome

The use of repaglinide might be associated with an increased incidence of acute coronary syndrome (e.g. myocardial infarction), see sections 4.8 and 5.1.

Concomitant use

Repaglinide should be used with caution or be avoided in patients receiving medicinal products which influence repaglinide metabolism (see section 4.5). If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products are known to influence repaglinide metabolism. Possible interactions should therefore 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 CYP2C8 as being the most important enzyme involved in repaglinide metabolism with CYP3A4 playing a minor role, but the relative contribution of CYP3A4

can be increased if CYP2C8 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 CYP2C8 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, clarithromycin, itraconazole, ketokonazole, trimethoprim, 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 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 section 4.3).

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, the concomitant use of trimethoprim with repaglinide should be avoided. If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed (see section 4.4).

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 two weeks after withdrawal of rifampicin where the inductive effect of rifampicin is no longer present. It cannot be excluded that other inducers, e.g. phenytoin, carbamazepine, phenobarbital, St John's wort, may have a similar effect.

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. In an interaction study in healthy volunteers, co-administration of 250 mg clarithromycin, a potent mechanism-based inhibitor of CYP3A4, 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.

In a study conducted in healthy volunteers, the concomitant administration of repaglinide (a single dose of 0.25 mg) and ciclosporin (repeated dose at 100 mg) 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 0.25 mg for repaglinide, the concomitant use of ciclosporin with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed (see section 4.4).

In an interaction study with healthy volunteers, co-administration of deferasirox (30 mg/kg/day, 4 days), a moderate inhibitor of CYP2C8 and CYP3A4, and repaglinide (single dose, 0.5 mg) resulted in an increase in repaglinide systemic exposure (AUC) to 2.3-fold (90% CI [2.03-2.63]) of control, a 1.6-fold (90% CI [1.42-1.84]) increase in C_{max}, and a small, significant decrease in blood glucose values. 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 section 4.4).

In an interaction study with healthy volunteers, co-administration of *clopidogrel* (300 mg loading dose), a CYP2C8 inhibitor, increased repaglinide exposure (AUC0–∞) 5.1-fold and continued administration (75 mg daily dose) increased repaglinide exposure (AUC0–∞) 3.9-fold. A small, significant decrease in blood glucose values was observed. Since the safety profile of the co-treatment has not been established in these patients, the concomitant use of clopidogrel and repaglinide should be avoided. If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed (see section 4.4).

β-blocking medicinal products 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.

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

Paediatric population

No interaction studies have been performed in children and adolescents.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no studies of repaglinide in pregnant women. Repaglinide should be avoided during pregnancy.

Breast-feeding

There are no studies in breast-feeding women. Repaglinide should not be used in breast-feeding women.

Fertility

Data from animal studies investigating effects on embryofetal and offspring development as well as excretion in milk is described in section 5.3.

4.7 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 whilst 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.

4.8 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 medicinal products 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) and not known (cannot be estimated from the available data).

Immune system disorders	Allergic reactions*	Very rare
Metabolism and nutrition disorders	Hypoglycaemia	Common
	Hypoglycaemic coma and hypoglycaemic unconsciousness	Not known
Eye disorders	Refraction disorder*	Very rare
Cardiac disorders	Cardiovascular disease	Rare
Gastrointestinal disorders	Abdominal pain, diarrhoea	Common
	Vomiting, constipation	Very rare
	Nausea	Not known
Hepatobiliary disorders	Abnormal hepatic function, increased liver enzymes*	Very rare
Skin and subcutaneous tissue disorders	Hypersensitivity*	Not known

* 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 commencement of treatment. Such disturbances have only been reported in very few cases after initiation of repaglinide treatment. No such cases have led to discontinuation of repaglinide treatment in clinical trials.

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 of the skin may occur as erythema, itching, rashes and urticaria. There is no reason to suspect cross-allergenicity with sulphonylurea due to the difference in chemical structure.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Drugs used in diabetes, other blood glucose lowering drugs, excl. insulins, ATC code: A10BX02

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.

One epidemiological study suggested an increased risk of acute coronary syndrome in repaglinide treated patients as compared to sulfonylurea treated patients (see sections 4.4 and 4.8).

5.2 Pharmacokinetic properties

Absorption

Repaglinide is rapidly absorbed from the gastrointestinal tract, which leads to a rapid increase in the plasma concentration of the active 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 the 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 1% 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 (4 mg 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 are available.

5.3 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 shown not to be teratogenic in animal studies. Embryotoxicity, abnormal limb development in rat foetuses and new born 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)
Calcium hydrogen phosphate, anhydrous
Maize starch
Polacrilin potassium
Povidone (polyvidone)
Glycerol 85%
Magnesium stearate
Meglumine
Poloxamer
Iron oxide, red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

The blister pack (aluminium/aluminium) contains 30, 90, 120 or 270 tablets, respectively.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/98/076/018-020, EU/1/98/076/022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 August 1998
Date of last renewal: 23 July 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARDS TO SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In case a Risk Management Plan is submitted to any regulatory authority the MAH must inform the Rapporteur.	N/A

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

NovoNorm 0.5 mg tablets
Repaglinide

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 0.5 mg of repaglinide

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
90 tablets
120 tablets
270 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/98/076/004 30 tablets
EU/1/98/076/005 90 tablets
EU/1/98/076/006 120 tablets
EU/1/98/076/023 270 tablets

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

novonorm 0.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

NovoNorm 0.5 mg tablets
Repaglinide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

NovoNorm 1 mg tablets
Repaglinide

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 1 mg of repaglinide

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
90 tablets
120 tablets
270 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/98/076/011 30 tablets
EU/1/98/076/012 90 tablets
EU/1/98/076/013 120 tablets
EU/1/98/076/024 270 tablets

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

novonorm 1 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

NovoNorm 1 mg tablets
Repaglinide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

NovoNorm 2 mg tablets
Repaglinide

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 2 mg of repaglinide

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
90 tablets
120 tablets
270 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/98/076/018 30 tablets
EU/1/98/076/019 90 tablets
EU/1/98/076/020 120 tablets
EU/1/98/076/022 270 tablets

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

novonorm 2 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

NovoNorm 2 mg tablets
Repaglinide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user
NovoNorm 0.5 mg tablets
NovoNorm 1 mg tablets
NovoNorm 2 mg tablets

Repaglinide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NovoNorm is and what it is used for

NovoNorm is an *oral antidiabetic medicine containing repaglinide* which helps your pancreas produce more insulin and thereby lower your blood sugar (glucose).

Type 2 diabetes is a disease in which your pancreas does not make enough insulin to control the sugar in your blood or where your body does not respond normally to the insulin it produces.

NovoNorm is used to control type 2 diabetes in adults as an add-on to diet and exercise: treatment is usually started if diet, exercise and weight reduction alone have not been able to control (or lower) your blood sugar. NovoNorm can also be given with metformin, another medicine for diabetes.

NovoNorm has been shown to lower the blood sugar, which helps to prevent complications from your diabetes.

2. What you need to know before you take NovoNorm

Do not take NovoNorm

- If you are **allergic** to repaglinide or any of the other ingredients in this medicine (listed in section 6).
- If you have **type 1 diabetes**.
- If the acid level in your blood is raised **(diabetic ketoacidosis).**
- If you have a **severe liver disease.**
- If you take **gemfibrozil** (a medicine used to lower increased fat levels in the blood).

Warnings and precautions
Talk to your doctor before taking NovoNorm:

- If you have **liver problems**. NovoNorm is not recommended in patients with moderate liver disease. NovoNorm should not be taken if you have a severe liver disease (see *Do not take NovoNorm*).
- If you have **kidney problems**. NovoNorm should be taken with caution.
- If 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 you are **under 18** or **over 75 years** of age. NovoNorm is not recommended. It has not been studied in these age groups.

Talk to your doctor if any of the above applies to you. NovoNorm may not be suitable for you. Your doctor will advise you.

Children and adolescents

Do not take this medicine if you are under 18 years of age.

If you get a hypo (low blood sugar)

You may get a hypo (short for hypoglycaemia) if your blood sugar gets too low. This may happen:
- If you take too much NovoNorm
- If you exercise more than usual
- If you take other medicines or suffer from liver or kidney problems (see other sections of *2. What you need to know before you take NovoNorm*).

The warning signs of a hypo may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.
If your blood sugar is low or you feel a hypo coming on: eat glucose tablets or a high sugar snack or drink, then rest.
When symptoms of hypoglycaemia have disappeared or when blood sugar levels are stabilised continue NovoNorm treatment.
Tell people you have diabetes and that if you pass out (become unconscious) due to a hypo, they must turn you on your side and get medical help straight away. They must not give you any food or drink. It could choke you.
- **If severe hypoglycaemia** is not treated, it can cause brain damage (temporary or permanent) and even death.
- **If you have a hypo** that makes you pass out, or a lot of hypos, talk to your doctor. The amount of NovoNorm, food or exercise may need to be adjusted.

If your blood sugar gets too high

Your blood sugar may get too high (hyperglycaemia). This may happen:
- If you take too little NovoNorm
- If you have an infection or a fever
- If you eat more than usual
- If you exercise less than usual.

The warning signs of too high blood sugar appear gradually. They include: increased urination; feeling thirsty; dry skin and dry mouth. Talk to your doctor. The amount of NovoNorm, food or exercise may need to be adjusted.

Other medicines and NovoNorm

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
You can take NovoNorm with metformin, another medicine for diabetes, if your doctor prescribes it.
If you take gemfibrozil (used to lower increased fat levels in the blood) you should not take NovoNorm.

Your body's response to NovoNorm may change if you take other medicines, especially these:
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta blockers (used to treat high blood pressure or heart conditions)
- ACE-inhibitors (used to treat heart conditions)
- Salicylates (e.g. aspirin)
- Octreotide (used to treat cancer)
- Nonsteroidal anti-inflammatory drugs (NSAID) (a type of painkillers)
- Steroids (anabolic steroids and corticosteroids – used for anemia or to treat inflammation)
- Oral contraceptives (birth control pills)
- Thiazides (diuretics or 'water pills')
- Danazol (used to treat breast cysts and endometriosis)
- Thyroid products (used to treat low levels of thyroid hormones)
- Sympathomimetics (used to treat asthma)
- Clarithromycin, trimethoprim, rifampicin (antibiotic medicines)
- Itraconazole, ketokonazole (antifungal medicines)
- Gemfibrozil (used to treat high blood fats)
- Ciclosporin (used to suppress the immune system)
- Deferasirox (used to reduce chronic iron overload)
- Clopidogrel (prevents blood clots)
- Phenytoin, carbamazepine, phenobarbital (used to treat epilepsy)
- St. John's wort (herbal medicine).

NovoNorm with alcohol

Alcohol can change the ability of NovoNorm to reduce the blood sugar. Watch for signs of a hypo.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

You should not take NovoNorm if you are pregnant or you are planning to become pregnant.

You should not take NovoNorm if you are breast-feeding.

Driving and using machines

Your ability to drive or use a machine may be affected if your blood sugar is low or high. Bear in mind that you could endanger yourself or others. Please ask your doctor whether you can drive a car if you:
- Have frequent hypos
- Have few or no warning signs of hypos.

3. How to take NovoNorm

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.
Your doctor will work out your dose.

- **The normal starting dose** is 0.5 mg before each main meal. Swallow the tablets with a glass of water immediately before or up to 30 minutes before each main meal.
- The dose may be adjusted by your doctor by up to 4 mg to be taken immediately before or up to 30 minutes before each main meal. The maximum recommended daily dose is 16 mg.

Do not take more NovoNorm than your doctor has recommended.

If you take more NovoNorm than you should

If you take too many tablets, your blood sugar may become too low, leading to a hypo. Please see *If you get a hypo* on what a hypo is and how to treat it.

If you forget to take NovoNorm

If you miss a dose, take the next dose as usual - do not double the dose.

If you stop taking NovoNorm

Be aware that the desired effect is not achieved if you stop taking NovoNorm. Your diabetes may get worse. If any change of your treatment is necessary contact your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Hypoglycaemia
The most frequent side effect is hypoglycaemia which may affect up to 1 in 10 patients (see *If you get a hypo* in section 2). Hypoglycaemic reactions are generally mild/moderate but may occasionally develop into hypoglycaemic unconsciousness or coma. If this happens, medical assistance is needed immediately.

Allergy
Allergy is very rare (may affect up to 1 in 10,000 patients). Symptoms such as swelling, difficulty in breathing, rapid heartbeat, feeling dizzy and sweating could be signs of anaphylactic reaction. Contact a doctor immediately.

Other side effects
Common (may affect up to 1 in 10 patients)
- Stomach pain
- Diarrhoea.

Rare (may affect up to 1 in 1,000 patients)
- Acute coronary syndrome (but it may not be due to the medicine).

Very rare (may affect up to 1 in 10,000 patients)
- Vomiting
- Constipation
- Visual disturbances
- Severe liver problems, abnormal liver function such as increased liver enzymes in your blood.

Frequency not known
- Hypersensitivity (such as rash, itchy skin, redening of the skin, swelling of the skin)
- Feeling sick (nausea).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store NovoNorm

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister foil after EXP. The expiry date refers to the last date of that month.

Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What NovoNorm contains

- The active substance is repaglinide.
- The other ingredients are microcrystalline cellulose (E460), calcium hydrogen phosphate anhydrous, maize starch, polacrilin potassium, povidone (polyvidone), glycerol 85%, magnesium stearate, meglumine, poloxamer, iron oxide yellow (E172) only in the 1 mg tablets and iron oxide red (E172) only in the 2 mg tablets.

What NovoNorm looks like and contents of the pack

NovoNorm tablets are round and convex and engraved with the Novo Nordisk logo (Apis bull). The strengths are 0.5 mg, 1 mg and 2 mg. 0.5 mg tablets are white, 1 mg tablets are yellow and 2 mg tablets are peach-coloured. Four blister pack sizes are available. Each pack contains 30, 90, 120 or 270 tablets.
Not all pack sizes may be marketed.

Marketing authorisation holder and manufacturer

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

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.