APPROVED PACKAGE INSERT

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

NovoNorm® 0,5 mg Tablets

NovoNorm® 1,0 mg Tablets

NovoNorm® 2,0 mg Tablets

COMPOSITION:

Each NovoNorm® 0,5 mg tablet contains: Repaglinide 0,5 mg.

Each NovoNorm® 1,0 mg tablet contains: Repaglinide 1 mg.

Each NovoNorm® 2,0 mg tablet contains: Repaglinide 2 mg.

NovoNorm® tablets contain the following inactive excipients: Microcrystalline cellulose (E460); Calcium hydrogen phosphate, anhydrous; Maize starch; Amberlite (polacrilin potassium); Povidone (polyvidone); Glycerol 85 %; Magnesium stearate; Meglumine; Poloxamer.

NovoNorm® 1,0 mg tablets also contain Iron Oxide Yellow (E172) as a colour pigment.

NovoNorm® 2,0 mg tablets also contain Iron Oxide Red (E172) as a colour pigment.

PHARMACOLOGICAL CLASSIFICATION:

A 21.2 Oral Hypoglycaemics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Repaglinide is a short acting oral hypoglycaemic agent of the meglitinide class, structurally unrelated to the sulphonylurea agents.

Repaglinide lowers the blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon the presence of functioning beta cells in the pancreatic islets.

In Type 2 diabetic patients (formerly known as non-insulin dependent diabetes mellitus or adult onset), the insulinotropic response to a meal occurred within 30 minutes after oral dose of NovoNorm®.

Plasma repaglinide levels decreased rapidly and low medicine concentrations were seen in the plasma of Type 2 diabetic patients 4 hours post administration.

A dose-related but not dose proportional decrease in blood glucose was demonstrated in Type 2 diabetic patients when administered dose from 0,5 - 4 mg NovoNorm®.

Pharmacokinetic properties:

Repaglinide is rapidly absorbed from the gastrointestinal tract. Peak plasma levels occur within 1 hour after administration.

After reaching a maximum, the plasma level decreases rapidly, and repaglinide is eliminated within 4 - 6 hours. In young healthy volunteers, the plasma elimination half-life is approximately 1 hour.

Repaglinide is characterised by a mean absolute bioavailability of 63 % (cv 11 %), low volume of distribution (approximately 30 litres into the tissues), and rapid elimination from the blood. A high inter-individual variability (60 %) in repaglinide plasma concentrations has been detected in clinical trials.

Repaglinide is highly bound to plasma proteins in humans (greater than 98 %).

Repaglinide is almost completely metabolised in the liver, and of the metabolites tested thus far, none have shown clinically relevant hypoglycaemic effect.

Repaglinide and its metabolites are excreted primarily via the bile. A small fraction (less than 8 %) of the administered dose appears in the urine. Less than 1 % of the parent medicine is recovered in faeces. Healthy volunteers were treated with regimen of 2 mg taken before each of 3 meals. There were no significant differences in repaglinide pharmacokinetics between the group of patients < 65 years of age and comparably sized group of patients ≥ 65 years of age. (See special populations, Geriatric).

Special Populations:

Paediatric:

No studies have been performed in paediatric patients.

Geriatric:

In repaglinide clinical studies of 24 weeks or greater duration, 415 patients were over 65 years of age. In one-year, active-controlled trials, no differences were seen in effectiveness or adverse events between these subjects and those less than 65 other than the expected age related increase in cardiovascular events observed for NovoNorm® and comparator medicines. There was no increase in frequency or severity of the hypoglycaemia in older subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals to NovoNorm® therapy cannot be ruled out.

Gender:

Comparison of pharmacokinetics in males and females showed the AUC over the 0,5 mg to 4 mg dose range to be 15 % to 70 % higher in females with Type 2 diabetes. This difference was not reflected in the frequency of hypoglycaemic episodes (male: 16 %; Female: 17 %) or other adverse events. With respect to the gender, no change in general dosage recommendation is indicated since dosage for each patient should be individualised to achieve optimal clinical response.

Renal insufficiency:

Single-dose and steady-state pharmacokinetics of repaglinide were evaluated in patients with various degrees of renal impairment. Measures of AUC and C_{max} after multiple dosing of 2 mg repaglinide were found to be higher in three groups of patients with reduced renal function ($AUC_{mild/moderate\ impairment}$: 90,8 ng/ml x hr; $AUC_{severe\ impairment}$: 137.7 ng/ml x hr; $AUC_{healthy}$: 29,1 ng/ml x hr; $C_{max,\ mild\ /moderate\ impairment}$: 46,7 ng/ml; $C_{max,\ severe\ impairment}$: 44,0 ng/ml; $C_{max\ healthy}$: 20,6 ng/ml). Repaglinide AUC is only weakly correlated to creatinine clearance.

Initial dosage adjustment does not appear to be necessary but subsequent increase in NovoNorm® should be made carefully in patients who have renal function impairment or

renal failure requiring haemodialysis.

Hepatic insufficiency:

A single dose, open label study was conducted in 12 healthy subjects and 12 patients with chronic liver disease (CLD) classified by caffeine clearance. Patients with moderate to severe impairment of liver function had higher and more prolonged serum concentrations with both total and unbound repaglinide than healthy subjects ($AUC_{healthy}$: 91,6 ng/ml x hr; $AUC_{CLD\ patients}$: 368,9 ng/ml x hr; $C_{max,\ healthy}$: 46,7 ng/ml; $C_{max,\ CLD\ patients}$: 105,4 ng/ml) AUC was statistically correlated with caffeine clearance. No difference in glucose profiles was observed across patient groups. Patient with impaired liver function may be exposed to higher concentrations of repaglinide and its associated metabolites than would patients with normal function receiving usual doses.

Therefore, NovoNorm® should be used cautiously in patients with impaired liver function. Longer intervals between dose adjustments should be utilised to allow full assessment of response.

INDICATIONS:

NovoNorm® (repaglinide) is indicated as an adjunct to diet and exercise to lower blood glucose in Type 2 diabetes mellitus patients whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise alone.

NovoNorm® may be used in combination with metformin or thiazolidinedione to lower blood glucose in patients whose glycaemia cannot be controlled by exercise, diet and either NovoNorm,® metformin or thiazolidinedione alone.

Combination therapy with NovoNorm® and insulin is indicated in Type 2 diabetes patients who are not satisfactorily controlled on sulphonylureas or NovoNorm® alone.

Use of NovoNorm® must be viewed by both the medical practitioner and the patient as a treatment in addition to diet and not as a substitute for diet, or a convenient mechanism for avoiding dietary restrain.

CONTRA-INDICATIONS:

- Known hypersensitivity to repaglinide or any of the excipients in NovoNorm®;
- Type 1 diabetes (Juvenile Insulin Dependent Diabetes Mellitus) ;
- Diabetes ketoacidosis, with or without coma;
- Children;
- Severe renal and hepatic impairment (See Pharmacological Action – Special Population, special warnings and precautions and Dosage and Directions for Use);
- Concomitant use of gemfibrozil;
- Concomitant use of deferasirox;
- Pregnancy and lactation

WARNINGS and SPECIAL PRECAUTIONS:

General:

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

NovoNorm® is capable of producing hypoglycaemia.

Mild hypoglycaemic reaction may be treated with oral intake of carbohydrates. Severe hypoglycaemic reaction will require an intravenous administration of glucose.
The symptoms of hypoglycaemia may include anxious feeling, dizziness, sweating, tremour, hunger and difficulty in concentration.

The blood glucose lowering effect of oral hypoglycaemic agents decreases in many patients over time. This may be due to progression of severity of diabetes or to diminished responsiveness to the product. This phenomenon is known as secondary failure, to distinguish it from primary failure, where the agent is ineffective in an individual patient when first given. Adjustment of dose and adherence to diet and exercise must be assessed before classifying a patient as a secondary failure.

NovoNorm® acts through a distinct site with a short action on the ß-cells.

Trials investigating the combination with other insulin secretagogues and acarbose have not been performed.

Combination treatment with metformin or thiazolidinedione or insulin is associated with increased risk of hypoglycaemia.

When a patient stabilised on any oral hypoglycaemic agent is exposed to stress such as fever, trauma, infection or surgery, a loss of glycaemic control may occur. At such times it may be necessary to discontinue NovoNorm® and treat with insulin on a temporary basis.

Specific patients groups:

No clinical studies have been conducted in patients with impaired hepatic function. No clinical studies have been performed in children and adolescents < 18 years old or in patients > 75 years of age. Therefore treatment is not recommended in these patient groups.

The administration of oral hypoglycaemic agents has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

Careful titration of the dose is advised in the elderly with impaired renal or hepatic function as elimination of NovoNorm® may be delayed in these patients (see Contra-indications).

Effects on ability to drive and use machines:

NovoNorm may influence the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycaemia whilst driving and using machines. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes hypoglycaemia.

INTERACTIONS:

A number of medicines are known to influence glucose metabolism, possible interactions should therefore be taken into account by the medical practitioner.

In vitro data indicate that NovoNorm® is metabolised predominantly by CYP2C8, but also by CYP3A4. NovoNorm® appears to be substrate for active hepatic uptake (organic anion transporting protein OATP1B1). Clinical data in healthy volunteers support CYP2C8 as being the most important enzyme involved in NovoNorm® metabolism with CYP3A4 playing minor role, but the relative contribution can be increased if CYP2C8 is inhibited.

Consequently metabolism and by that the clearance of NovoNorm® may be altered by medicines that influence these cytochrome P-450 enzyme via inhibition or induction. Medicines that inhibit OATP1B1 (e.g. ciclosporin) may likewise have the potential to increase plasma concentration of repaglinide.

The following substances may enhance the hypoglycaemic effect of NovoNorm®: gemfibrozil, clarithromycin, itraconazole, rifampicin, deferasirox, clopidogrel, ketoconazole,

trimethoprim, ciclosporin, other antidiabetic agents, monoamine oxide inhibitors (MAOI), beta blocking agents, angiotensin converting enzyme (ACE) – inhibitors and angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory agents (NSAIDs), salicylates, alcohol, octreotide and anabolic steroids.

Co-administration of gemfibrozil (600 mg twice daily) an inhibitor of CYP2C8, and NovoNorm® (as single dose of 0,25 mg) increased the NovoNorm® 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 NovoNorm®, and plasma NovoNorm®concentration at 7 hr was increased 28,6-fold by gemfibrozil. The concomitant use of gemfibrozil and NovoNorm® is contra-indicated.

In an interaction study in healthy volunteers, co-administration of 250 mg clarithromycin, a potent mechanism-based inhibitor of CYP3A4, slightly increased the NovoNorm® 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 C_{max} by 1,6-fold. The exact mechanism of this interaction is not clear.

Ciclosporin (100 mg), an inhibitor of CYP3A4 and a strong OATP1B1 inhibitor, increased the repaglinide (0,25 mg) C_{max} 1,8-fold and the AUC 2,5-fold in an interaction study with healthy volunteers. In an interaction study with healthy volunteers, co-administration of deferasirox (30 mg/kg/day, 4 days), a weak inhibitor of CYP2C8 and CYP3A4, and repaglinide (single dose, 0,5mg) resulted in an increase in repaglinide systemic exposure (AUC) to 2,3-fold of control, an increase in C_{max} of 62 %, and a small, significant decrease in blood glucose values (see contraindications).
dose, 0,5mg) resulted in an increase in repaglinide systemic exposure (AUC) to 2,3-fold of control, an increase in C_{max} of 62%, and a small, significant decrease in blood glucose values. (see contraindications).

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 was observed.

The effect of ketoconazole, a potent inhibitor of CYP3A4, on the pharmacokinetics of NovoNorm® has been studied in healthy subjects. Co-administration of 200 mg of ketoconazole increased the NovoNorm® AUC by 1,5-fold and Cmax by 1,6-fold with profiles of blood glucose concentrations altered by less than 8 % when administered concomitantly (a single dose of 4 mg NovoNorm®).

Co-administration of trimethoprim (160 mg twice daily) a week CYP2C8 inhibitor and NovoNorm® (a single dose of 0,25 mg) resulted in slight increases in NovoNorm® 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.

Rifampicin, a potent inducer of CYP3A4, but also CYP2C8 acts both an inducer and inhibitor of the metabolism of NovoNorm®. Seven days pre-treatment with rifampicin (600 mg) followed by co-administration of NovoNorm® (a single dose of 4 mg) at day 7 resulted in a 1,5-fold lower AUC (effect of combined induction and inhibition). When NovoNorm® was given 24 hours after the last rifampicin dose, a 1,8-fold reduction of the NovoNorm® AUC was observed (effect of induction alone). Concomitant use of rifampicin and NovoNorm® might therefore induce a need for NovoNorm® dose adjustment which should be based on carefully monitored blood glucose concentrations at both initiation of rifampicin treatment (acute inhibition) maintenance dosing (mixing 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.

Co-administration of cimetidine, nifedipine, oestrogen or simvastatin with NovoNorm®, all

CYP3A4 substrates, did not significantly alter the pharmacokinetic parameters of NovoNorm®. NovoNorm® (2 mg, 3 times daily) had no clinically relevant effect on the pharmacokinetic properties of digoxin (0,25 mg, 4 times daily), theophylline (300 mg, 2 times daily) nor warfarin at steady state, when administered to healthy volunteers.

Thus, dosage adjustment of digoxin, theophylline or warfarin does not appear to be necessary for co-administration with NovoNorm®.

In an interaction study with healthy volunteers, co administration of clopidogrel (300 mg on day 1, followed by 75 mg daily for two consecutive days), a CYP2C8 inhibitor, and repaglinide (single dose of 0.25 mg on day 1 and day 3) resulted in an increase in repaglinide systemic exposure (AUC0-∞) to 5.1-fold and 3.9-fold respectively, and a small, significant decrease in blood glucose values. If repaglinide and clopidogrel are used concomitantly, careful clinical and blood glucose monitoring should be performed.

The following substances may reduce the hypoglycaemic effect of NovoNorm®: Oral contraceptives, rifampicin, barbiturates, carbamazepine, thiazides, corticosteroids, danazol, thyroid hormones and sympathomimetics.

Beta-blocking agents may mask the symptoms of hypoglycaemia. Alcohol may intensify and prolong the hypoglycaemic effect of NovoNorm®. When these medications are administered to or withdrawn from a patient receiving NovoNorm®, the patient should be observed closely for loss of glycaemic control.

When NovoNorm® is used together with other medicines that are mainly secreted by the bile, any potential interaction should be considered.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established. NovoNorm® is excreted in milk. NovoNorm® should not be used during pregnancy and should not be used in women breastfeeding their infants (see contra-indications).

DOSAGE AND DIRECTIONS FOR USE:

There is no fixed dosage regimen for the management of Type 2 diabetes with NovoNorm®. NovoNorm® is given preprandially and is titrated individually to optimise the glycaemic control. In addition to the usual 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 may also be of value in monitoring the patient's response to therapy. Periodic monitoring is necessary to detect inadequate lowering of blood glucose at the maximum recommended 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).

NovoNorm® should be taken 15 minutes before main meals but time may vary from immediately preceding main meal to as long as 30 minutes before main meals.

Initial Dose:

The recommended starting dose is 0,5 mg, given with meals (preprandially).

The dosage should be determined by the medical practitioner, according to the patient's requirements.

About one or two weeks should elapse between titration steps (as determined by blood

glucose response).

Maintenance:

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

Dosages in the elderly and patients with impaired renal and hepatic failure, see CONTRA-INDICATIONS and WARNINGS and SPECIAL PRECAUTIONS.

Patients receiving other oral hypoglycaemic agents (OHAs):

Patients can be transferred directly from other hypoglycaemic agents to NovoNorm®.

However, no exact dosage relationship exists between NovoNorm® and the other oral hypoglycaemic agents. The recommended maximum starting dose of patients transferred to NovoNorm® is 1 mg before main meals.

NovoNorm® may be used in combination with metformin or thiazolidinedione to lower blood glucose in patients whose glycaemia cannot be controlled by exercise, diet and either NovoNorm,® metformin or thiazolidinedione alone. In this case, the dosage of metformin or thiazolidinedione should be maintained and NovoNorm® administered concomitantly. The starting dose of NovoNorm® is 0,5 mg, 3 times daily preprandially; titration is according to blood glucose response as for monotherapy.

NovoNorm®-insulin combination therapy:

Combination therapy with NovoNorm® and insulin may be used in secondary failure patients. Patients controlled on maximum dose may benefit from treatment with bedtime insulin. Insulin doses should be titrated according to therapeutic response and in accordance with recommendations for the marketed product. Periodic adjustments of

insulin may be necessary during maintenance as guided by blood glucose and HbA1c levels.

SIDE EFFECTS:

The following side effects have been observed:

Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1000); very rare (< 1/10 000)

Immune system disorders:

Very rare:

Generalised hypersensitivity reactions (e.g. anaphylactic reactions) or immunological reactions such as vasculitis may occur.

***Metabolism and Nutrition disorders*:**

Common:

Hypoglycaemia

Not known:

Hypoglycaemic coma and hypoglycaemic unconsciousness

***Visual Disturbances*:**

Very rare:

Changes in blood glucose levels may result in transient visual disturbances.

Gastro–intestinal:

Common:

Abdominal pain and diarrhoea.

Very rare:

Vomiting and constipation.

Not known:

Nausea

***Liver disorders*:**

Very rare:

Hepatic enzymes increased

Cases of increase in liver enzymes have been reported. Most cases were mild and transient, and very few patients discontinued treatment due to increase in liver enzymes.

Abnormal hepatic function

Cases of severe hepatic dysfunction have been reported.

***Skin and subcutaneous tissue disorders*:**

Not known

Allergy

Hypersensitivity reactions of the skin may occur as itching, rashes and urticaria.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The symptoms of overdosage are related to the glucose lowering effects of NovoNorm®. Hypoglycaemia may be expected to range from mild to severe.

Hypoglycaemic symptoms include dizziness, sweating, tremor, headache and palpitations.

Should these symptoms occur, adequate action should be taken to correct the low blood glucose (oral carbohydrates).

More severe hypoglycaemia with seizures, loss of consciousness or coma should be treated with i.v. glucose (up to 50 ml of 50 % glucose may be necessary). In situations where i.v. administration of glucose is impractical or not feasible, glucagon 0,5 mg to 2 mg subcutaneously or intramuscularly may be given.

IDENTIFICATION:

NovoNorm® 0,5 mg: White, round, biconvex tablets, engraved with Novo Nordisk logo (Apis Bull).

NovoNorm® 1,0 mg: Yellow, round, biconvex tablets, engraved with Novo Nordisk logo (Apis Bull).

NovoNorm® 2,0 mg: Peach, round, biconvex tablets, engraved with Novo Nordisk logo (Apis Bull).

PRESENTATION:

Push-through aluminium/aluminium blister packs containing 30, 90, or 120 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25°C. Protect from moisture.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBERS:

NovoNorm® 0,5 mg: 33/21.2/0078

NovoNorm® 1,0 mg: 33/21.2/0079

NovoNorm® 2,0 mg: 33/21.2/0080

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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2196

DATE OF PUBLICATION OF THE PACKAGE INSERT

Date on the registration certificate: 06 September 1999

Date of the most recently revised package insert as approved by council:

11 December 2019