

## PRODUCT MONOGRAPH

**GlucoNorm<sup>®</sup>**

(repaglinide tablets)

0.5 mg, 1 mg and 2 mg

Oral antidiabetic Agent

**Novo Nordisk Canada Inc.**  
300 – 2680 Skymark Ave.  
Mississauga, Ontario  
Canada L4W 5L6  
novonordisk.ca

Submission Control No: 182759

Date of Revision: 03 June 2015

## Table of Contents

<b>PART I: HEALTH PROFESSIONAL INFORMATION.....</b>	<b>3</b>
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS .....	4
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	7
DRUG INTERACTIONS .....	11
DOSAGE AND ADMINISTRATION .....	16
OVERDOSAGE .....	18
ACTION AND CLINICAL PHARMACOLOGY .....	18
STORAGE AND STABILITY.....	21
DOSAGE FORMS, COMPOSITION AND PACKAGING .....	21
<b>PART II: SCIENTIFIC INFORMATION .....</b>	<b>22</b>
PHARMACEUTICAL INFORMATION.....	22
CLINICAL TRIALS .....	23
DETAILED PHARMACOLOGY .....	26
TOXICOLOGY .....	28
REFERENCES .....	34
<b>PART III: CONSUMER INFORMATION.....</b>	<b>36</b>

## GlucoNorm® Tablets

(repaglinide)

### PART I: HEALTH PROFESSIONAL INFORMATION

**Table 1 - SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
oral	0.5 mg, 1 mg and 2 mg tablet	Microcrystalline cellulose (E460), calcium hydrogen phosphate anhydrous, maize starch, amberlite (polacrilin potassium), povidone (polyvidone), glycerol 85%, magnesium stearate, meglumine, poloxamer (0.5 mg), yellow iron oxide (1 mg), or red iron oxide (2 mg).  <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

### INDICATIONS AND CLINICAL USE

GlucoNorm® (repaglinide) is indicated:

- As an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone.
- In combination therapy with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise plus metformin monotherapy.
- In combination with rosiglitazone in patients who show intolerance to metformin or for whom metformin is contraindicated, when diet and exercise plus rosiglitazone or GlucoNorm® monotherapy do not result in adequate glycemic control.

If glucose control has not been achieved after a suitable trial of combination therapy, consideration should be given to discontinuing these drugs and other antihyperglycemic agents including insulin. Judgments should be based on regular clinical and laboratory evaluations.

In initiating treatment for type 2 diabetes, diet and exercise should be emphasized as the primary form of treatment. Caloric restriction, weight loss and exercise are essential in the obese diabetic patient. Proper dietary management and exercise alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. In addition to regular physical activity, cardiovascular risk factors should be identified and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, GlucoNorm® should be

discontinued. The use of other oral blood glucose-lowering agent or insulin should be considered. Use of GlucoNorm<sup>®</sup> must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of GlucoNorm<sup>®</sup>.

**Geriatrics (>65 years of age):** GlucoNorm<sup>®</sup> can be used in elderly above 65 years of age without further monitoring or special care except in those with renal, hepatic or other problems (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions**). GlucoNorm<sup>®</sup> is not recommended for use in elderly above 75 years of age due to lack of data on safety and/or efficacy (see **WARNINGS AND PRECAUTIONS – Special Populations**).

**Pediatrics (<18 years of age):** Safety and effectiveness of GlucoNorm<sup>®</sup> has not been established in patients under 18 years of age. Use of GlucoNorm<sup>®</sup> is not recommended in pediatric patients (see **WARNINGS AND PRECAUTIONS – Special Populations**).

## **CONTRAINDICATIONS**

GlucoNorm<sup>®</sup> (repaglinide) is contraindicated:

- In patients with known hypersensitivity to the drug or any of its components. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- In patients with diabetic ketoacidosis, with or without coma.
- In patients with Type 1 diabetes.
- In patients with severe liver disease.
- In patients who are using gemfibrozil (see **ADVERSE REACTIONS** and **DRUG INTERACTIONS**).
- In patients who are using clopidogrel (see **DRUG INTERACTIONS**).

## **WARNINGS AND PRECAUTIONS**

### **General**

GlucoNorm<sup>®</sup> (repaglinide) is effective as a prandial glucose regulator and should be taken before meals (2, 3 or 4 times a day preprandially). Therefore, if a meal is missed or delayed, the dose of GlucoNorm<sup>®</sup> should be skipped or delayed as appropriate.

### **Carcinogenesis and Mutagenesis**

See **TOXICOLOGY**.

### **Cardiovascular**

The administration of insulin secretagogues in general has been reported to be associated with increased cardiovascular (CV) mortality as compared to treatment with diet alone or diet plus insulin. In controlled clinical trials comparing GlucoNorm<sup>®</sup> (repaglinide) with glyburide and other sulfonylureas, there was no excess mortality with GlucoNorm<sup>®</sup> use. The overall incidence

of serious CV events including death was 4.2 per 100 patient years.

In clinical trials, the incidence of serious cardiovascular treatment emergent adverse events was higher for repaglinide than for glyburide but lower than that for glipizide (see **ADVERSE REACTIONS** and **CLINICAL TRIALS**).

### **Endocrine and Metabolism**

**Hypoglycemia:** GlucoNorm<sup>®</sup> is capable of inducing hypoglycemia. Proper patient selection, dosage, and instructions to the patient are important to avoid hypoglycemic episodes.

Hepatic insufficiency may cause elevated repaglinide levels in the blood and may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions (see **WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic**). GlucoNorm<sup>®</sup> is contraindicated in patients with severe liver disease (see **CONTRAINDICATIONS**).

Elderly, debilitated or malnourished patients and those with adrenal, pituitary or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs.

Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Hypoglycemia is more likely to occur when caloric intake is deficient or when meals are skipped. Given the preprandial dosing regimen, patients taking GlucoNorm<sup>®</sup> can adjust dosing according to their changing meal patterns, thereby reducing the risk of hypoglycemia when meals are missed (see **DOSAGE AND ADMINISTRATION**).

Hypoglycemia is also more likely to occur after strenuous or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

**Loss of control of blood glucose:** When a patient, stabilized on GlucoNorm<sup>®</sup> is exposed to stress such as fever, trauma, infection, or surgery, a loss of control of blood glucose may occur. At such times, it may be necessary to temporarily discontinue GlucoNorm<sup>®</sup> and administer insulin.

### **Hepatic/Biliary/Pancreatic**

Patients with impaired liver function may be exposed to higher concentrations of repaglinide than would patients with normal liver functions receiving usual doses. GlucoNorm<sup>®</sup> should be used cautiously in patients with impaired liver function. Longer intervals between dose adjustments should be utilized to allow full assessment of response (see **WARNINGS AND PRECAUTIONS – Endocrine and Metabolism** and **Monitoring and Laboratory Tests, ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions**). GlucoNorm<sup>®</sup> is contraindicated in patients with severe liver disease (see **CONTRAINDICATIONS**).

### **Neurologic**

Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of glucose solution, followed by a continuous infusion, according to standard medical practice.

## **Renal**

### **Renal insufficiency**

Typically, GlucoNorm<sup>®</sup> does not require initial dose adjustment in patients with reduced kidney function. However, subsequent increases in GlucoNorm<sup>®</sup> should be made carefully in patients with type 2 diabetes who have renal function impairment or renal failure requiring hemodialysis (see **ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions**).

## **Pre-operative considerations**

See **WARNINGS AND PRECAUTIONS – Endocrine and Metabolism, Loss of control of blood glucose**.

## **Special Populations**

**Pregnant Women:** GlucoNorm<sup>®</sup> is not recommended for use during pregnancy. The safety of GlucoNorm<sup>®</sup> in pregnant women has not been established (see **TOXICOLOGY**).

**Nursing Women:** The safety of GlucoNorm<sup>®</sup> in nursing women has not been established. In rat reproduction studies, measurable levels of repaglinide were detected in the breast milk of the dams and lowered blood glucose levels were observed in the pups. It is not known whether GlucoNorm<sup>®</sup> is excreted in human milk. GlucoNorm<sup>®</sup> is not recommended in nursing women because the potential for hypoglycemia in nursing infants may exist (see **TOXICOLOGY**).

**Pediatrics (<18 years of age):** The use of GlucoNorm<sup>®</sup> is not recommended in pediatric patients. The safety and effectiveness in pediatrics has not been established. No studies of GlucoNorm<sup>®</sup> have been performed in pediatric patients.

**Geriatrics (>65 years of age):** No special dose titration is necessary in elderly patients. 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 GlucoNorm<sup>®</sup> and comparator drugs. There was no increase in frequency or severity of hypoglycemia 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 GlucoNorm<sup>®</sup> therapy cannot be ruled out, in particular in those with renal, hepatic and other problems (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

No specific clinical studies have been conducted in type 2 patients >75 years of age.

**Hepatic Impairment:** GlucoNorm<sup>®</sup> should be used cautiously in patients with impaired liver function. GlucoNorm<sup>®</sup> is contraindicated in patients with severe liver disease (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic** and **ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions**).

**Renal Impairment:** Dosage adjustment should be made cautiously in patients with type 2 diabetes mellitus who have renal function impairment or renal failure requiring hemodialysis (see **WARNINGS AND PRECAUTIONS – Renal** and **ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions**).

### **Monitoring and Laboratory Tests**

In addition to self-monitoring of blood and/or urinary glucose, the patient's blood glucose should be monitored by the physician to determine the minimum effective dose for the patient. Periodic monitoring is necessary to detect primary failure (inadequate lowering of blood glucose at the maximum recommended dose of medication), and to detect secondary failure (loss of adequate blood glucose-lowering after an initial period of effectiveness).

For patients with an increased risk of hypoglycemia or at risk of losing blood glucose control, a closer glucose monitoring should be considered (see **WARNINGS AND PRECAUTIONS – Endocrine and Metabolism**). Glycosylated hemoglobin levels (HbA<sub>1c</sub>) are of value in monitoring the patient's longer term response to therapy.

Hepatic function should be assessed before initiating the therapy and periodically in patients with impaired hepatic function (see **WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic**).

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The most frequently reported Adverse Drug Reaction (ADR) is hypoglycemia. The occurrence of such reactions depends, as for every diabetes therapy, on individual factors, such as dietary habits, dosage, exercise and stress.

In one-year comparator trials, the incidence of individual events was not greater than 1% except for chest pain (1.8%) and angina (1.8%). The overall incidence of other cardiovascular events (hypertension, abnormal EKG, myocardial infarction, arrhythmias, and palpitations) was  $\leq 1\%$  and not different for GlucoNorm7 and the comparator drugs.

The incidence of serious cardiovascular adverse events added together, including ischemia, was slightly higher for repaglinide (4%) than for sulfonylurea drugs (3%) in controlled comparator clinical trials. In 1-year controlled trials, GlucoNorm7 treatment was not associated with excess mortality rates compared to rates observed with other oral hypoglycemic agent therapies.

## **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

GlucNorm<sup>®</sup> (repaglinide) has been administered to 2931 individuals worldwide during clinical trials. Approximately 1500 of these individuals with type 2 diabetes have been treated for at least 3 months, 1000 for at least 6 months, and 800 for at least 1 year. The majority of these individuals (1228) received GlucNorm<sup>®</sup> in one of five 1-year, active-controlled trials, where GlucNorm<sup>®</sup> was administered three times a day with meals in doses of 0.5-4 mg per meal. The comparator drugs in these 1-year trials were oral sulfonylurea drugs (SU).

GlucNorm<sup>®</sup> was well-tolerated in these clinical trials and analysis of adverse events shows no dose relationship to rate of occurrence. The adverse event profile for the GlucNorm<sup>®</sup> and SU groups in these trials was generally comparable over one year. The rate of withdrawals due to adverse events was 13% among GlucNorm<sup>®</sup> treated patients and 14% among SU-treated patients. The most common adverse events leading to withdrawal were hyperglycemia, hypoglycemia, and related symptoms. Mild or moderate hypoglycemia occurred in 16% of GlucNorm<sup>®</sup> patients and 20% of sulfonylurea patients.

The table below lists common clinical trial adverse drug reactions for GlucNorm<sup>®</sup> patients compared to both placebo (in trials less than 6 months duration) and to glyburide, gliclazide and glipizide in one year trials. The clinical trial adverse drug reactions profile of GlucNorm<sup>®</sup> was generally comparable to that for SU.

**Table 2 – TREATMENT-EMERGENT ADVERSE EVENTS WITH POSSIBLE OR PROBABLE RELATIONSHIP-REPORTED AT A FREQUENCY OF ≥ 1% WITH GLUCONORM<sup>®</sup>**

EVENT	GlucNorm <sup>®</sup> n = 1228	SU n = 597	GlucNorm <sup>®</sup> n = 352	PLACEBO n = 108
	Active controlled studies		Placebo controlled studies	
	n (%)	n (%)	n (%)	n (%)
<b>Eye disorders</b>				
Vision abnormal	5 (<1.0)	2 (<1.0)	7 (2.0)	1 (<1.0)
<b>General disorders</b>				
Fatigue	21 (1.7)	4 (<1.0)	9 (2.6)	3 (2.8)
<b>Gastrointestinal disorders</b>				
Diarrhoea	11 (<1.0)	7 (1.2)	6 (1.7)	-*
Constipation	7 (<1.0)	6 (1.0)	4 (1.1)	-*

EVENT	GlucNorm® n = 1228	SU n = 597	GlucNorm® n = 352	PLACEBO n = 108
	Active controlled studies		Placebo controlled studies	
Abdominal pain	12 (1.0)	6 (1.0)	4 (1.1)	1 (<1.0)
Flatulence	7 (<1.0)	2 (<1.0)	4 (1.1)	.*
Nausea	12 (1.0)	7 (1.2)	4 (1.1)	2 (1.9)
Dyspepsia	13 (1.1)	5 (<1.0)	.*	.*
<b>Nervous system disorders</b>				
Headache	28 (2.3)	12 (2.0)	9 (2.6)	1 (<1.0)
Dizziness	16 (1.3)	9 (1.5)	8 (2.3)	3 (2.8)
Tremor	14 (1.1)	6 (1.0)	1 (<1.0)	.*
<b>Metabolism and nutrition disorders</b>				
Hypoglycemia	179 (14.6)	102 (17.1)	24 (6.8)	2 (1.9)
Hyperglycaemia	35 (2.9)	18 (3.0)	4 (1.1)	5 (4.6)
<b>Skin and subcutaneous tissue disorders</b>				
Sweating increased	13 (1.1)	4 (<1.0)	.*	.*

\* No events observed

### **Less Common Clinical Trial Adverse Drug Reactions (<1%)**

#### **Cardiovascular disorders**

In one-year comparator trials, the incidence of individual cardiovascular events considered possibly or probably related to trial drug was less than 1%.

The incidence of all observed serious cardiovascular adverse events (i.e. including events not considered possibly or probably related to trial drug) added together, including ischemia, was slightly higher for repaglinide (4%) than for sulfonylurea drugs (3%) in controlled comparator clinical trials. In 1-year controlled trials, GlucNorm® treatment was not associated with excess mortality rates compared to rates observed with other oral hypoglycemic agent therapies.

**Table 3 – Summary of Serious Cardiovascular Events (% of total patients with events)**

	GlucNorm®	SU*
<b>Total Exposed</b>	1228	498
Serious CV Events	4%	3%
Cardiac Ischemic Events	2%	2%
Deaths due to CV Events	0.5%	0.4%

\* glyburide and glipizide

**Eye disorders:** Very rare visual disturbance

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.

**Gastro-intestinal disorders:** Vomiting

**Hepatobiliary disorders:** Severe hepatic dysfunction

In very rare cases, severe hepatic dysfunction has been reported. However, other causes were implicated in these cases and causal relationship with repaglinide has not been established.

**Immune system disorders:** Allergy

Generalized hypersensitivity reactions or immunological reactions such as vasculitis may occur very rarely.

**Skin and subcutaneous tissue disorders:** Hypersensitivity reactions of skin may occur as erythema, itching, rashes and urticaria.

**Abnormal Hematologic and Clinical Chemistry Findings:** Less common adverse clinical and laboratory events observed in clinical trials, including events not considered possibly or probably related to trial drug included elevated liver enzymes, bilirubinaemia, thrombocytopenia and leukopenia.

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 an increase in liver enzymes.

### **Post-Market Adverse Drug Reactions**

**Eye Disorders:** visual disturbance

**Gastrointestinal Disorders:** abdominal pain, diarrhea, vomiting, constipation, nausea

**Hepatobiliary Disorders:** hepatic function abnormal, hepatic enzymes increased

**Immune System Disorders:** allergy, anaphylactic reactions have been observed in very few cases.

**Metabolism and Nutrition Disorders:** hypoglycemia, hypoglycemic coma, hypoglycemic unconsciousness

Serious hypoglycemic events have been reported in patients co-administered repaglinide and gemfibrozil. Concomitant use of repaglinide and gemfibrozil is contraindicated (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

**Skin and subcutaneous disorders:** hypersensitivity (erythema, itching, rash, urticaria)

## DRUG INTERACTIONS

### Serious Drug Interactions

The concomitant use of gemfibrozil and repaglinide is contraindicated (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS – Drug-Drug Interactions**).

The concomitant use of clopidogrel and repaglinide is contraindicated (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS – Drug-Drug Interactions**).

### Overview

Drug interaction studies performed in healthy volunteers show that repaglinide had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline, or warfarin at steady state. Dosage adjustment of these compounds when co-administered with GlucoNorm<sup>®</sup> is therefore not necessary. Co-administration of cimetidine, nifedipine, estrogen, or simvastatin with GlucoNorm<sup>®</sup> did not significantly alter the absorption and disposition of repaglinide.

### Drug-Drug Interactions

*The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).*

The drugs were studied in healthy volunteers with co-administration of repaglinide.

**Table 4: Established or Potential Drug-Drug Interactions**

<b>Drug Class</b>	<b>Ref</b>	<b>Effect</b>	<b>Clinical Comment</b>
Clopidogrel	CT	<u>300 mg clopidogrel</u> ↑ AUC by 5.1-fold ↑ C <sub>max</sub> by 2.5-fold  <u>75 mg clopidogrel</u> ↑ AUC by 3.9-fold ↑ C <sub>max</sub> by 2.0-fold	Co-administration of clopidogrel (a CYP2C8 inhibitor; 300 mg on day 1 followed by 75 mg daily for two consecutive days) and repaglinide (single dose of 0.25 mg on day 1 and day 3), in healthy volunteers, increased repaglinide systemic exposure (AUC <sub>0-∞</sub> ) by 5.1-fold and 3.9-fold, and C <sub>max</sub> by 2.5-fold and 2.0-fold, respectively. The elimination half-life of repaglinide also increased from 1.6 hours to 2.3 hours (300 mg clopidogrel) and to 2.0 hours (75 mg clopidogrel), along with a significant decrease in blood glucose levels. In CYP2C8*1/*4 polymorphic individuals, repaglinide AUC <sub>0-∞</sub> increased up to 8.8-fold and 7.4-fold, on co-administration, respectively. The concomitant use of repaglinide and clopidogrel is contraindicated (see <b>CONTRAINDICATIONS</b> ).

<b><u>Drug Class</u></b>	<b><u>Ref</u></b>	<b><u>Effect</u></b>	<b><u>Clinical Comment</u></b>
Gemfibrozil	CT	↑ AUC by 8.1-fold ↑ C <sub>max</sub> by 2.4-fold	Co-administration of gemfibrozil (600 mg), an inhibitor of CYP2C8 and OATP1B1, and a single dose of 0.25 mg repaglinide (after 3 days of twice-daily 600 mg gemfibrozil) resulted in an 8.1-fold higher repaglinide AUC and prolonged repaglinide half-life from 1.3 to 3.7 hr. The concomitant use of gemfibrozil and repaglinide is contraindicated (see <b>CONTRAINDICATIONS</b> ).
Gemfibrozil and itraconazole	CT	↑ AUC by 19-fold	Co-administration of both gemfibrozil and itraconazole with repaglinide resulted in a 19-fold higher repaglinide AUC and prolonged repaglinide half-life from 1.3 to 6.1 hr. Plasma repaglinide concentration at 7 h increased 28.6-fold with gemfibrozil co-administration and 70.4-fold with the gemfibrozil-itraconazole combination. Concomitant use of gemfibrozil and repaglinide is contraindicated (see <b>CONTRAINDICATIONS</b> ).
ACE inhibitors	T	May potentiate the hypoglycemic effect of repaglinide.	The patient should be observed for hypoglycemia.
Anabolic steroids	T	May potentiate the hypoglycemic effect of repaglinide.	The patient should be observed for hypoglycemia. When these drugs are either administered or withdrawn from a patient receiving GlucoNorm <sup>®</sup> , the patient should be observed for loss of glycemic control.
Beta-blockers	T	May potentiate the hypoglycemic effect of repaglinide. Beta-blockers may also mask the symptoms of hypoglycaemia.	The patient should be observed for hypoglycemia. When these drugs are either administered or withdrawn from a patient receiving GlucoNorm <sup>®</sup> , the patient should be observed for loss of glycemic control.
Clarithromycin	CT	↑ AUC by 1.4-fold ↑ C <sub>max</sub> by 1.7-fold	Co-administration of 250 mg clarithromycin, a potent CYP3A4 inhibitor, and a single dose of 0.25 mg repaglinide (after 4 days of twice daily clarithromycin 250 mg) resulted in a 40% and 67% increase in repaglinide AUC and C <sub>max</sub> , respectively. The increase in repaglinide AUC was from 5.3 ng/mL*hr to 7.5 ng/mL*hr and the increase in C <sub>max</sub> was

<b>Drug Class</b>	<b>Ref</b>	<b>Effect</b>	<b>Clinical Comment</b>
			from 4.4 ng/mL to 7.3 ng/mL.
Cortico-steroids	T	May reduce the hypoglycemic effect of repaglinide and potentiate hyperglycemia.	The patient should be observed for hyperglycaemia. When these drugs are either administered or withdrawn from a patient receiving GlucoNorm <sup>®</sup> , the patient should be observed for loss of glyceemic control.
Cyclosporine	CT	↑ AUC by 2.5-fold ↑ C <sub>max</sub> by 1.8-fold	Co-administration of cyclosporine, an inhibitor of CYP3A4 and strong OATP1B1 inhibitor, caused an increase in repaglinide (0.25 mg) mean peak plasma concentrations of 175% and the total area under the plasma concentration-time curve was 244% of that in the placebo phase.
Danazol	T	May reduce the hypoglycemic effect of repaglinide and potentiate hyperglycemia.	The patient should be observed for hyperglycaemia. When these drugs are either administered or withdrawn from a patient receiving GlucoNorm <sup>®</sup> , the patient should be observed for loss of glyceemic control.
Deferasirox	CT	↑ AUC by 2.3-fold ↑ C <sub>max</sub> by 0.62-fold	Co-administration in healthy volunteers of deferasirox (30 mg/kg/day for 4 days) and repaglinide (single dose of 0.5 mg) resulted in an increase in repaglinide systemic exposure (AUC) to 2.3-fold of control and an increase in C <sub>max</sub> of 62%, and a small, significant decrease in blood glucose values. If repaglinide and deferasirox are used concomitantly, decreasing the dose of repaglinide should be considered and patient blood glucose levels carefully monitored.
Itraconazole	CT	↑ AUC by 1.4-fold	Co-administration of itraconazole, a CYP3A4 inhibitor, and a single dose of 0.25 mg repaglinide (on the third day of a regimen of 200 mg initial dose, twice-daily 100 mg itraconazole) resulted in a 1.4-fold higher repaglinide AUC.
Ketoconazole	CT	↑ AUC by 1.2-fold ↑ C <sub>max</sub> by 1.2-fold	Co-administration of 200 mg ketoconazole, a potent and competitive inhibitor of CYP3A4, and a single dose of 2 mg repaglinide in healthy subjects (after 4 days of once daily ketoconazole 200 mg) resulted in a 15% and 16% increase in repaglinide. The increases were from 20.2 ng/mL to 23.5 ng/mL for C <sub>max</sub> and from 38.9 ng/mL*hr to 44.9

<b>Drug Class</b>	<b>Ref</b>	<b>Effect</b>	<b>Clinical Comment</b>
			ng/mL*hr for AUC.
Monoamine Oxidase Inhibitors (MAOI)	T	May potentiate the hypoglycemic effect of repaglinide.	The patient should be observed for hypoglycemia. When these drugs are either administered or withdrawn from a patient receiving GlucoNorm <sup>®</sup> , the patient should be observed for loss of glycemic control.
Octreotide	T	May potentiate the hypoglycemic effect of repaglinide.	The patient should be observed for hypoglycemia. When these drugs are either administered or withdrawn from a patient receiving GlucoNorm <sup>®</sup> , the patient should be observed for loss of glycemic control.
Oral contraceptives (ethinyl estradiol/levonorgestrel)	CT		A pharmacokinetic clinical trial in healthy volunteers demonstrated that concomitant oral contraceptive administration (ethinyl estradiol/levonorgestrel) did not alter repaglinide's total bioavailability to a clinically relevant degree, although peak levels of repaglinide occurred earlier. Repaglinide had no clinically meaningful effect upon bioavailability of levonorgestrel but effects on ethinyl estradiol bioavailability cannot be excluded.
Other antidiabetic agents	T	May potentiate the hypoglycemic effect of repaglinide.	The patient should be observed for hypoglycemia.
Phenytoin, carbamazepine and phenobarbital	T	May reduce the hypoglycemic effect of repaglinide and potentiate hyperglycemia.	The patient should be observed for hyperglycaemia. When these drugs are either administered or withdrawn from a patient receiving GlucoNorm <sup>®</sup> , the patient should be observed for loss of glycemic control.
Rifampicin	CT	<u>Co-administration:</u> ↓ AUC by 32% - 48% ↓ C <sub>max</sub> by 26% - 17%  <u>Monoadministration of repaglinide after 7 days of rifampicin:</u> ↓ AUC by 80% ↓ C <sub>max</sub> by 79%	Co-administration of 600 mg rifampicin and a single dose of 4 mg repaglinide (after 6 days of once daily rifampicin 600 mg) resulted in a 32% and 26% decrease in repaglinide AUC and C <sub>max</sub> , respectively. The decreases were from 40.4 ng/mL to 29.7 ng/mL for C <sub>max</sub> and from 56.8 ng/mL*hr to 38.7 ng/mL*hr for AUC.  In another study co-administration of 600 mg

<b>Drug Class</b>	<b>Ref</b>	<b>Effect</b>	<b>Clinical Comment</b>
			<p>rifampicin and a single dose of 4 mg repaglinide (after 6 days of once daily rifampicin 600 mg) resulted in a 48% and 17% decrease in repaglinide AUC and C<sub>max</sub>, respectively. The decreases were from 54 ng/mL*hr to 28 ng/mL*hr for AUC and from 35 ng/mL to 29 ng/mL for C<sub>max</sub>.</p> <p>Repaglinide administered by itself (after 7 days of once daily rifampicin 600 mg) resulted in an 80% and 79% decrease in repaglinide AUC and C<sub>max</sub>, respectively. The decreases were from 54 ng/mL*hr to 11 ng/mL*hr for AUC and from 35 ng/mL to 7.5 ng/mL for C<sub>max</sub>.</p>
Salicylates e.g. aspirin and non-steroidal anti-inflammatory agents (NSAIDs)	T	May potentiate the hypoglycemic effect of repaglinide.	<p>The patient should be observed for hypoglycemia.</p> <p>When these drugs are either administered or withdrawn from a patient receiving GlucoNorm<sup>®</sup>, the patient should be observed for loss of glycemic control.</p>
Sympathomimetics	T	May reduce the hypoglycemic effect of repaglinide and potentiate hyperglycemia.	<p>The patient should be observed for hyperglycaemia.</p> <p>When these drugs are either administered or withdrawn from a patient receiving GlucoNorm<sup>®</sup>, the patient should be observed for loss of glycemic control.</p>
Thiazides	T	May reduce the hypoglycemic effect of repaglinide and potentiate hyperglycemia.	<p>The patient should be observed for hyperglycaemia.</p> <p>When these drugs are either administered or withdrawn from a patient receiving GlucoNorm<sup>®</sup>, the patient should be observed for loss of glycemic control.</p>
Thyroid hormones	T	May reduce the hypoglycemic effect of repaglinide and potentiate hyperglycemia.	<p>The patient should be observed for hyperglycaemia.</p>
Trimethoprim	CT	<p>↑ AUC by 1.6-fold</p> <p>↑ C<sub>max</sub> by 1.4-fold</p>	<p>Co-administration of trimethoprim, 160 mg and a single dose of 0.25 mg repaglinide (after 2 days of twice daily and one dose on the third day of trimethoprim 160 mg) resulted in a 61% and 41% increase in</p>

<b><u>Drug Class</u></b>	<b><u>Ref</u></b>	<b><u>Effect</u></b>	<b><u>Clinical Comment</u></b>
			repaglinide AUC and C <sub>max</sub> , respectively. The increase in AUC was from 5.9 ng/mL*hr to 9.6 ng/mL*hr and the increase in C <sub>max</sub> was from 4.7 ng/mL to 6.6 ng/mL. The concomitant use of trimethoprim with repaglinide should be avoided.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

### **Drug-Food Interactions**

Grapefruit may increase the plasma concentration of repaglinide. In a study with healthy volunteers where grapefruit juice was consumed 2 hours prior to repaglinide intake, a 13% increase in AUC was observed. No other interactions with food have been established.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

### **Drug-Lifestyle Interactions**

Alcohol may enhance and/or prolong the hypoglycemic effect of repaglinide.

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia. The advisability of driving should be considered in these circumstances.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

There is no fixed dosage regimen for the management of type 2 diabetes with GlucoNorm<sup>®</sup> (repaglinide).

GlucoNorm<sup>®</sup> doses are usually taken 15 minutes before the meal but time may vary from immediately before the meal to as long as 30 minutes before the meal. Patients who skip a meal (or add an extra meal) should be instructed to skip (or add) a dose for that meal.

Short-term administration of GlucoNorm<sup>®</sup> may be sufficient during periods of transient loss of control in patients usually controlled by their diet.

## **Recommended Dose and Dosage Adjustment**

### **Initiation Dose**

For patients not previously treated with antidiabetic agents or whose HbA<sub>1c</sub> <8%, the starting dose should be 0.5 mg with each meal preprandially.

For patients previously treated with blood glucose-lowering drugs or whose HbA<sub>1c</sub> is ≥ 8%, the initial dose is 1 or 2 mg with each meal preprandially.

### **Transfer from other therapies**

When GlucoNorm<sup>®</sup> is used to replace therapy with other oral hypoglycemic agents, GlucoNorm<sup>®</sup> may be started on the day after the final dose is given. Patients should then be observed carefully for hypoglycemia due to potential overlapping of drug effects. When transferred from longer half-life sulfonylurea agents (e.g., chlorpropamide) to GlucoNorm<sup>®</sup>, close monitoring may be indicated for up to one week or longer.

### **Titration**

Dosing adjustments should be determined by blood glucose response, usually fasting blood glucose. The preprandial dose should be doubled up to 4 mg until satisfactory blood glucose response is achieved. A minimum of one week should elapse between titration steps to assess response after each dose adjustment.

### **Maintenance**

The recommended dose range is 0.5 mg to 4.0 mg taken with meals. GlucoNorm<sup>®</sup> offers flexible dietary options and may be dosed preprandially 2, 3 or 4 times a day in response to changes in the patient's meal pattern. The recommended maximum daily dose is 16 mg.

Long-term efficacy should be monitored by measurement of HbA<sub>1c</sub> levels every 3 months.

Failure to follow an appropriate dosage regimen may precipitate hypoglycemia or hyperglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy, including hypoglycemia.

For patients maintained in tight glucose control, GlucoNorm<sup>®</sup> treatment has less associated risk of hypoglycemia when meals are missed than does treatment with agents with a longer half-life.

### **Combination Therapy**

If GlucoNorm<sup>®</sup> monotherapy does not result in adequate glycemic control, metformin or rosiglitazone may be added. Or, if metformin or rosiglitazone monotherapy does not provide adequate control, GlucoNorm<sup>®</sup> may be added. The starting dose and dose adjustments for GlucoNorm<sup>®</sup> combination therapy is the same as for GlucoNorm<sup>®</sup> monotherapy. The dose of each drug should be carefully adjusted to determine the minimal dose required to achieve the desired pharmacologic effect. Failure to do so could result in an increase in the incidence of hypoglycemic episodes. Appropriate monitoring of FPG and HbA<sub>1c</sub> measurements should be used to ensure that the patient is not subjected to excessive drug exposure or increased probability of secondary drug failure.

### **Missed Dose**

If a dose is missed, the next dose should be taken as usual. The dose should not be doubled.

### **OVERDOSAGE**

In a clinical trial, patients received increasing doses of GlucoNorm<sup>®</sup> (repaglinide) up to 80 mg a day for 14 days. There were few adverse effects other than those associated with the intended pharmacodynamic effect of lowering blood glucose. Hypoglycemia did not occur when meals were given with these high doses.

Hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery. There is no evidence that repaglinide is dialyzable using hemodialysis.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

GlucoNorm<sup>®</sup> (repaglinide) is an oral blood glucose-lowering drug used in the management of type 2 diabetes mellitus. Repaglinide is a short-acting insulin secretagogue which lowers blood glucose levels (as measured by HbA<sub>1c</sub> and fasting plasma glucose) and is effective in regulating meal-related (prandial) glucose loads. Repaglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta cells in the pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations.

Repaglinide is chemically unrelated to oral sulfonylurea insulin secretagogues used in the treatment of type 2 diabetes.

Repaglinide closes ATP-dependent potassium channels in the  $\beta$ -cell membrane by binding at characterizable sites. This potassium channel blockade depolarizes the  $\beta$ -cell which leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion. The ion channel mechanism is highly tissue selective with low affinity for heart and skeletal muscle.

### **Pharmacokinetics**

**Absorption:** After oral administration, repaglinide is rapidly and completely absorbed from the gastrointestinal tract. After single and multiple oral doses in healthy subjects or in patients, peak drug levels ( $C_{max}$ ) occur within 1 hour ( $T_{max}$ ). Repaglinide is rapidly eliminated from the blood

stream with a half-life of approximately 1 hour. The mean absolute bioavailability is 56%. When repaglinide was given with food, the mean  $T_{max}$  was not changed, but the mean  $C_{max}$  and AUC (area under the plasma concentration-time curve) were decreased 20% and 12.4%, respectively.

**Distribution:** After intravenous (IV) dosing in healthy subjects, the volume of distribution at steady state ( $V_{SS}$ ) was approximately 31 L, and the total body clearance (CL) was 38 L/h. Protein binding and binding to human serum albumin was greater than 98%.

**Metabolism:** Repaglinide is completely metabolized by oxidative biotransformation and direct conjugation with glucuronic acid after either an IV or oral dose. The major metabolites are an oxidized dicarboxylic acid ( $M_2$ ), the aromatic amine ( $M_1$ ) and the acyl glucuronide ( $M_7$ ). The cytochrome P-450 enzyme system, specifically 2C8 and 3A4 has been shown to be involved in the N-dealkylation of repaglinide to  $M_2$  and the further oxidation to  $M_1$ . Metabolites do not contribute to the glucose-lowering effect of repaglinide.

**Excretion:** Within 96 hours after dosing with  $^{14}C$ -repaglinide as a single oral dose, approximately 90% of the radiolabel was recovered in the feces and 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound. The major metabolite ( $M_2$ ) accounted for 60% of the administered dose. Less than 2% of parent drug was recovered in feces.

**Pharmacokinetic parameters:** Data indicate that repaglinide did not accumulate in serum. Repaglinide demonstrated pharmacokinetic linearity over the 0.5 - 4 mg dose range.

The pharmacokinetic parameters of repaglinide obtained from a single-dose, crossover study in healthy subjects and from a multiple-dose, parallel, dose-proportionality (0.5, 1, 2 and 4 mg) study in patients with Type 2 diabetes are summarized below:

**Table 5 – Pharmacokinetic parameters of GlucoNorm<sup>®</sup>**

PARAMETER	PATIENTS WITH Type 2 diabetes <sup>a</sup>
<b>AUC<sub>0-24 hr</sub> (ng/mLxh):</b> 0.5 mg 1.0 mg 2.0 mg 4.0 mg	<b>Mean (SD):</b> 68.9 (154.4) 125.8 (129.8) 152.4 (89.6) 447.4 (211.3)
<b>C<sub>max</sub><sub>0-5 hr</sub> (ng/mL):</b> 0.5 mg 1.0 mg 2.0 mg 4.0 mg	<b>Mean (SD):</b> 9.8 (10.2) 18.3 (9.1) 26.0 (13.0) 65.8 (30.1)
<b>T<sub>max</sub><sub>0-5 hr</sub> (h):</b> 0.5 to 4 mg	<b>Means (SD range)</b> 1.0 to 1.4 (0.3 to 0.5)
<b>T<sub>2</sub> (h):</b> 0.5 to 4 mg	<b>Means (Indiv. Range)</b> 1.0 to 1.4 (0.4 to 8.0)
CL based on i.v. (L/h)	38 (16)

PARAMETER	PATIENTS WITH Type 2 diabetes <sup>a</sup>
V <sub>SS</sub> based on i.v. (L)	31 (12)
AbsBio (%)	56 (9)

a: dose preprandially three times daily

CL = Total body clearance

V<sub>ss</sub> = Volume of distribution at steady state

AbsBio = Absolute bioavailability

**Variability:** The intra-individual and inter-individual variabilities (coefficient of variation) in AUC were 36% and 69%, respectively after multiple dosing of repaglinide tablets (0.25 to 4 mg with each meal) in patients.

### **Special Populations and Conditions**

**Geriatrics:** Healthy volunteers were treated with a 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 a comparably sized group of patients ≥65 years of age.

**Gender:** A 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 hypoglycemic episodes (male: 16%; female: 17%) or other adverse events. With respect to gender, no change in general dosage recommendation is indicated since dosage for each patient should be individualized to achieve optimal clinical response.

**Race:** No pharmacokinetic studies to assess the effects of race have been performed, but in a U.S. 1-year study in patients with type 2 diabetes, the blood glucose-lowering effect was comparable between Caucasians (n=297) and African-Americans (n=33). In a U.S. dose-response study, there was no apparent difference in exposure (AUC) between Caucasians (n=74) and Hispanics (n=33).

**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 of both total and unbound repaglinide than healthy subjects (AUC<sub>healthy</sub>: 91.6 ng/mL\*h; AUC<sub>CLD</sub> patients: 368.9 ng/mL\*h; C<sub>max, healthy</sub>: 46.7 ng/mL; C<sub>max, CLD</sub> patients: 105.4 ng/mL). AUC was statistically correlated with caffeine clearance. No difference in glucose profiles was observed across patient groups. Patients with impaired liver function may be exposed to higher concentrations of repaglinide and its associated metabolites than would patients with normal liver function receiving the same doses.

**Renal Insufficiency:** Single-dose and steady state pharmacokinetics of repaglinide have been evaluated in patients with various degrees of renal impairment. Repaglinide was found to be well tolerated in all groups. Measures of AUC and C<sub>max</sub> after multiple dosing of 2 mg repaglinide were found to be higher in three groups of patients with reduced renal function (AUC<sub>mild/moderate</sub> impairment: 90.8 ng/mL\*hr to AUC<sub>severe</sub> impairment: 137.7 ng/mL\*hr versus AUC<sub>healthy</sub>: 29.1

ng/mL\*hr; C<sub>max</sub>, mild/moderate impairment: 46.7 ng/mL to C<sub>max</sub>, severe impairment: 44.0 ng/mL versus C<sub>max</sub>, healthy: 20.6 ng/mL). Repaglinide AUC is only weakly correlated to creatinine clearance.

**Genetic Polymorphism:** In healthy subjects, polymorphism in the SLCO1B1 gene (c.521T>C) encoding for the OATP1B1 transporter has been observed to lead to approximately 72% higher exposure (AUC). Polymorphism in CYP2C8 (CYP2C8\*3) has been studied in different studies in healthy subjects. The CYP2C8\*3 allele has been found to have either no effect or been associated with an approximately 50% lower exposure (AUC). The observed effects are explaining factors for the observed inter individual variability together with the variability in the expression of metabolizing enzymes.

### **STORAGE AND STABILITY**

GlucNorm<sup>®</sup> (repaglinide) should be stored at 15°C - 25°C. Protect from moisture.

Keep out of reach of children.

Unused medication should not be disposed of down the drain or in household garbage.

### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

GlucNorm<sup>®</sup> (repaglinide) tablets are supplied as unscored, biconvex tablets available in 0.5 mg (white), 1.0 mg (yellow) and 2.0 mg (peach) strengths. Tablets are embossed with the Novo Nordisk (Apis) bull symbol and coloured to indicate strength. All strengths are available in bottles of 100 tablets.

**Non-medicinal ingredients:** : microcrystalline cellulose (E460), calcium hydrogen phosphate anhydrous, maize starch, amberlite (polacrillin potassium), povidone (polyvidone), glycerol 85%, magnesium stearate, meglumine, poloxamer (0.5 mg), yellow iron oxide (1 mg), or red iron oxide (2 mg).

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

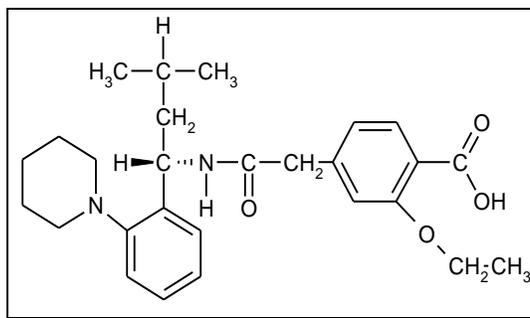
Proper name: Repaglinide

Chemical name: (+)-2-Ethoxy- $\alpha$ [[*(S)*- $\alpha$ -isobutyl-*o*-piperidinobenzyl] carbamoyl]-*p*-toluic acid

Molecular formula: C<sub>27</sub>H<sub>36</sub>N<sub>2</sub>O<sub>4</sub>

Molecular weight: 452.6

Structural formula:



#### Physicochemical properties:

Repaglinide is a white to off-white powder. It is practically insoluble in water, freely soluble in methanol and freely soluble in chloroform. Repaglinide has a pH of 5.0-7.0, a melting point of 132-136°C and its pKa is: pKa<sub>1</sub>= 3.9 and pKa<sub>2</sub>=6.1

## CLINICAL TRIALS

### Study demographics and trial design

A four-week, double-blind, placebo-controlled dose-response trial was conducted in patients with type 2 diabetes using doses ranging from 0.25 to 4 mg taken with each of three meals. GlucoNorm<sup>®</sup> therapy resulted in dose-proportional glucose-lowering over the full dose range. Plasma insulin levels increased after meals and reverted toward baseline before the next meal. Most of the fasting blood glucose-lowering effect was demonstrated within 1-2 weeks.

In a double-blind, placebo-controlled, 3-month dose titration study, GlucoNorm<sup>®</sup> or placebo doses for each patient were increased weekly from 0.25 mg through 0.5, 1, and 2 mg, to a maximum of 4 mg, until a fasting plasma glucose (FPG) level <8.9 mmol/L was achieved or the maximum dose reached. The dose that achieved the targeted control or the maximum dose was continued to end of study. FPG and 2-hour post-prandial glucose (PPG) increased in patients receiving placebo and decreased in patients treated with repaglinide. Differences between the repaglinide- and placebo-treated groups were -3.41 mmol/L (FPG) and -5.78 mmol/L (PPG). The between-group change in HbA<sub>1c</sub>, which reflects long-term glycemic control, was 1.7% units.

**Table 6 – GlucoNorm<sup>®</sup> vs. Placebo Treatment: Mean FPG, PPG and HbA<sub>1c</sub>**

FPG, PPG, and HbA <sub>1c</sub>						
	FPG (mmol/L)		PPG (mmol/L)		HbA <sub>1c</sub> (%)	
	<u>PL</u>	<u>R</u>	<u>PL</u>	<u>R</u>	<u>PL</u>	<u>R</u>
<b>Baseline</b>	11.96	12.23	13.62	14.54	8.1	8.5
<b>Change from Baseline (at last visit)</b>	1.68	-1.72*	3.14	-2.64*	1.1	-0.6*

PL = placebo, R = repaglinide

\* p# 0.05 for between group difference

Another double-blind, placebo-controlled trial was carried out in 362 patients treated for 24 weeks. The efficacy of 1 and 4 mg preprandial doses was demonstrated by lowering of fasting blood glucose and by HbA<sub>1c</sub> at the end of the study. HbA<sub>1c</sub> for the GlucoNorm<sup>®</sup> treated groups (1 and 4 mg groups combined) at the end of the study was decreased compared to the placebo-treated group in previously naïve patients and in patients previously treated with oral hypoglycemic agents by 2.1% units and 1.7% units, respectively. In this fixed-dose trial, patients who were naïve to oral hypoglycemic agent therapy and patients in relatively good glycemic control at baseline (HbA<sub>1c</sub> below 8%) showed greater blood glucose-lowering including a higher frequency of hypoglycemia. Patients who were previously treated and who had baseline HbA<sub>1c</sub>

≥ 8% reported hypoglycemia at the same rate as patients randomized to placebo. There was no average gain in body weight when patients previously treated with oral hypoglycemic agents were switched to GlucoNorm<sup>®</sup>. The average weight gain in patients treated with GlucoNorm<sup>®</sup> and not previously treated with sulfonylurea drugs was 3.3%.

The dosing of GlucoNorm<sup>®</sup> relative to meal-related insulin release was studied in three trials including 58 patients. Glycemic control was maintained during a period in which the meal and dosing pattern was varied (2, 3, or 4 meals per day; before meals x 2, 3, or 4) compared with a period of 3 regular meals and 3 doses per day (before meals x 3). It was also shown that GlucoNorm<sup>®</sup> can be administered at the start of a meal, 15 minutes before, or 30 minutes before the meal with the same blood glucose lowering effect.

GlucoNorm<sup>®</sup> was compared to other insulin secretagogues in 1-year controlled trials to demonstrate comparability of efficacy and safety. Hypoglycemia was reported in 16% of 1228 GlucoNorm<sup>®</sup> patients, 20% of 417 glyburide patients, and 19% of 81 glipizide patients. Of GlucoNorm<sup>®</sup> treated patients with symptomatic hypoglycemia, none developed coma or required hospitalization.

GlucoNorm<sup>®</sup> was studied in combination with metformin in 83 patients not satisfactorily controlled on exercise, diet, and metformin alone. Combination therapy with GlucoNorm<sup>®</sup> and metformin resulted in synergistic improvement in glycemic control compared to repaglinide or metformin monotherapy. HbA<sub>1c</sub> was improved by 1% unit and FPG decreased by an additional 1.94 mmol/L.

**Table 7 – GlucoNorm7 and Metformin Therapy: Mean HbA<sub>1c</sub> and FPG - Changes from Baseline after 3 Months Treatment**

	GlucoNorm7	Combination	Metformin
n	28	27	27
HbA <sub>1c</sub> (% units)	-0.38	-1.41*	-0.33
FPG (mmol/L)	0.49	-2.18*	-0.25

\* p# 0.05 for comparison between combination and both monotherapies

A combination therapy regimen of GlucoNorm<sup>®</sup> and rosiglitazone was compared to monotherapy with either agent alone in a 24-week trial that enrolled 252 patients previously treated with sulfonylurea or metformin (HbA<sub>1c</sub> > 7.0%). Combination therapy resulted in significantly greater improvement in glycemic control as compared to monotherapy. The glycemic effects of the combination therapy were dose-sparing with respect to both total daily GlucoNorm<sup>®</sup> dosage and total daily rosiglitazone dosage. A greater efficacy response of the combination therapy group was achieved with half the median daily dose of GlucoNorm<sup>®</sup> and rosiglitazone, as compared to the respective monotherapy groups. Mean weight increases associated with combination, GlucoNorm<sup>®</sup> and rosiglitazone therapy were 4.4 kg, 1.6 kg, and 2.3 kg, respectively.

**Table 8 - GlucoNorm<sup>®</sup> and rosiglitazone Therapy: Mean HbA<sub>1c</sub> and FPG - Changes from Baseline After 24 Weeks of Therapy**

	GlucoNorm 7	Combination	Rosiglitazone
n	59	126	55
HbA <sub>1c</sub> (% units)	-0.17	-1.43*	-0.56
n	57	122	56
FPG (mmol/L)	-3.01	-5.24*	-3.70

\* p<0.001 for comparison between combination and both monotherapies

### **Combination therapy with Rosiglitazone**

During a 24-week treatment clinical trial-of GlucoNorm<sup>®</sup>-rosiglitazone combination therapy (a total of 127 patients in combination therapy), hypoglycemia (blood glucose < 2.78mmol/L) occurred in 9% of combination therapy patients in comparison to 6% for GlucoNorm<sup>®</sup> monotherapy, and 2% for rosiglitazone monotherapy.

Peripheral edema was reported in 5 out of 127 GlucoNorm<sup>®</sup>-rosiglitazone combination therapy patients and 2 out of 62 rosiglitazone monotherapy patients, with no cases reported in this trial for GlucoNorm<sup>®</sup> monotherapy. There were no patients treated with GlucoNorm<sup>®</sup>-rosiglitazone therapy that reported episodes of edema with congestive heart failure.

Mean change in weight from baseline was +4.4 kg for GlucoNorm<sup>®</sup>-rosiglitazone therapy. There were no patients on GlucoNorm<sup>®</sup>-rosiglitazone combination therapy who had elevations of liver transaminases (defined as 3 times the upper limit of normal levels).

**Table 9 - GlucoNorm<sup>®</sup> and rosiglitazone Therapy: Events of hypoglycemia, peripheral edema and weight change**

	GlucoNorm <sup>®</sup>	Combination	Rosiglitazone
Minor hypoglycemic episode (blood glucose < 2.78mmol/L)	6%	9%	2%
Peripheral edema	0%	3.9%	3.2%
Weight change at end of study (24 weeks)	+1.6 kg	+4.4 kg	+2.3 kg

### **Cardiovascular**

The observed difference in the incidence of serious cardiovascular treatment emergent adverse events was higher for repaglinide than for glyburide but lower for glipizide and was not statistically significant when adjustments for baseline differences in prior medical history and predisposing conditions were made. In part, differences in baseline ECG, cardiovascular medical history and baseline cholesterol may have contributed to the difference in rates. When comparing GlucoNorm<sup>®</sup> to the sulfonylurea drugs as a whole, no statistically significant differences were found either for serious cardiovascular (CV) events or for all CV events. Dose analyses revealed no increase in CV risk with increasing doses of GlucoNorm<sup>®</sup>.

See also **ADVERSE REACTIONS**.

## DETAILED PHARMACOLOGY

### ANIMAL STUDIES:

#### Pharmacodynamics:

**Table 10 – Animal Pharmacology models and study results**

Test	Species/ Cellular Material	Route	Results and Conclusions
Hypoglycemic effect, comparison with AG-EE 388 ZW	Rat/Chbb:Thom (female)	p.o. i.v.	Intravenous administration of repaglinide or racemic mixture demonstrated a significant hypoglycemic effect in rats beginning at a dose of 0.01% mg/kg (racemic mixture) and 0.003 mg/kg (repaglinide). The ED <sub>10</sub> was 2-5 Φg/kg. There was no hypoglycemic activity following oral administration up to 1.0 mg/kg.
Hypoglycemic effect, comparison with AG-EE 388 ZW	Dog/Chbb: Beagle (female)	p.o.	In dogs, oral administration of repaglinide resulted in significant hypoglycemic activity and increased plasma insulin levels. The ED <sub>10</sub> was 5.6 Φg/kg.
Antihyperglycemic effects, comparison with glyburide	Normal and diabetic rats (male, 6-8/group)	p.o. i.v.	Repaglinide 10 times more potent than glyburide following both oral and intravenous administration. The duration of action and maximal efficacy, however, were similar (maximum effect at 120 mins for oral and 60 mins for i.v. administration).
<b>Profile in vivo- Rat</b>			
Insulin-stimulated glucose uptake, comparison with glyburide and placebo	Perifused rat hind limb (Wistar rats, male, 4/group)	--	Sensitivity to insulin in skeletal muscles not altered by either repaglinide or glyburide.
Evaluation of the effect of repaglinide and glyburide in rats with chronic renal dysfunction	Nephrectomized rat (male)	p.o.	No significant differences in dynamic profile compared to normal rats with either drug.
Hypoglycemic activity of AG-EE 388 ZW and its metabolites	Rat (female, Wistar)	i.v.	Metabolism of the racemic compound did result in active hypoglycemic metabolites. None of the metabolites exhibited an activity that was equal to or greater than the parent compound and they do not contribute to the hypoglycemic effect of the racemic compound.
<b>In vitro mechanism of action studies</b>			
Effects of repaglinide and glyburide on ATP-sensitive K <sup>+</sup> channels and intracellular [Ca <sup>2+</sup> ] using patch clamp techniques and digital Ca <sup>2+</sup> imaging	Newborn rat islets and mouse βTC3 cells	--	Equipotent with glyburide with respect to inhibition of beta-cell ATP-sensitive K <sup>+</sup> -channel and stimulation of an increase in [Ca <sup>2+</sup> ] (Both compounds causing dose-dependent inhibition and subsequent calcium influx).
Characterization of binding sites in β cells	Rat βTC3 cells and membranes	--	A unique binding profile different from SUs glyburide, glipizide, tolbutamide, glimepiride. Higher affinity to a binding site in βTC3 cells than SUs.

Test	Species/ Cellular Material	Route	Results and Conclusions
Regulation of ATP sensitive K <sup>+</sup> -channel by repaglinide and glyburide through different binding sites	Intact βTC3	--	Repaglinide and glyburide regulate the ATP-sensitive K <sup>+</sup> -channel through different binding sites in the β-cells. These sites are not equally dependent upon ADP and ATP.
Insulinotropic action: modulation by activator of ATP-sensitive K <sup>+</sup> -channel and high extracellular [K <sup>+</sup> ].	Rat pancreatic islets (female rats)	--	The insulinotropic action of repaglinide is mainly attributable to a primary block of ATP-sensitive K <sup>+</sup> -channels
Effect on glucose-stimulated insulin release in metabolic stressed mouse islets.	Mouse islets treated with Dinitrophenol (DNP) by perfusion	--	DNP-treated cells did not influence the activity of repaglinide but did affect glyburide and glibornuride. Repaglinide normalizes a situation of metabolic stress in isolated mouse islets, in contrast to glyburide and glibornuride.
Effect on glucose-stimulated insulin release in normal mouse islet.	Mouse islets	--	Repaglinide is 3-5 times more potent than glyburide. Activity of repaglinide is more dependent on presence of D-glucose than glyburide.
Profile <i>in vitro</i> . Effect on direct exocytosis. Binding characteristics to whole murine β-cells (βTC3 cells)	β-cells	--	Repaglinide had contrary to glyburide no direct effect on exocytosis. Three binding sites were identified. Findings suggest that repaglinide possesses both structural and mechanistic properties which are distinct from glyburide.
Effect on Ba <sup>2+</sup> -induced insulin release, comparison with meglitinide analogues	Rat islets isolated from pancreas	--	Insulinotropic action of meglitinide and repaglinide is due to primary and direct action on ATP-sensitive K <sup>+</sup> -channels as opposed to being primarily attributable to an intracellular redistribution of Ca <sup>2+</sup> ions.
Ionophoretic activity, comparison with meglitinide analogues	Artificial membrane model	--	Each hypoglycemic agent was able to cause translocation of <sup>45</sup> Ca and <sup>22</sup> Na from an aqueous solution into an immiscible organic phase. Ionophoretic activity did not closely parallel the insulinotropic potential of these compounds. Therefore, the ionophoretic capacity may not represent an essential determinant of the insulin-releasing action.
Insulinotropic activity, comparison with meglitinide and its analogues	Rat islets of Langerhans	--	Repaglinide the second most potent drug in its ability to evoke a secretory response in the islet cells. It is a potent insulin secretagogue. Augmented insulin release evoked by exogenous glucose.
Effect on biosynthetic activity	Rat islets	--	Repaglinide did not affect adversely glucose-stimulated protein and proinsulin biosynthesis. Repaglinide may offer the advantage over hypoglycemic SUs to preserve nutrient - stimulated biosynthetic activity in β-cells.
Relationship between reversibility and insulin releasing potency	Perifused rat islets	--	No parallelism between insulinotropic potency and reversibility of cationic and secretory effects
Effect on malate dehydrogenase, comparison with AG-EE 624 ZW	Mouse islets	--	No effect on activity or sub-cellular localization of enzymes with either compound
Pharmascreen Testing	<i>In vivo</i> : mouse	p.o.	Anti-hyperglycemic action.

Test	Species/ Cellular Material	Route	Results and Conclusions
Biochemical Testing	<i>In vitro</i> : isolated guinea pig trachea	--	No extra-pancreatic effect. Closure of ATP-sensitive K <sup>+</sup> -channel. Clean profile i.e. only high affinity in one receptor assay.

## TOXICOLOGY

### Acute Toxicity:

Repaglinide did not have significant acute oral toxicity in the rat; the LD<sub>50</sub> was >3000 mg/kg for males and between 2500-3000 mg/kg for females. Intravenous administration of repaglinide to rats resulted in LD<sub>50</sub> values of >50 mg/kg for males and 20-50 mg/kg for females. Clinical signs were similar to those seen following oral administration.

Dogs were more sensitive than rats. Deaths occurred in dogs at both 300 & 1000 mg/kg.

Both species had signs suggesting CNS effects, and included decreased activity; ptosis and hypothermia in the rat; and tremor, emesis, and staggering in the dog. No drug-induced lesions were observed for either species at necropsy.

**Table 11 - Long-Term Toxicity Studies**

Species/Strain Initial Group	Dosing Method	Duration of Treatment (w)	Dose (mg/kg/day)	Results
<b>Subchronic Toxicity</b>				
Mouse: CD-1 5M, 5F/group, 4 w old	Diet	8	0, 380, 480, 600, 750, 1000 (380 dose increased to 1500 at week 6)	<u>Deaths</u> : No treatment related effects <u>Clinical Signs</u> : No treatment related effects <u>Conclusions</u> : No treatment related effects.
Mouse Chbb:NMRI  10M,10F/dose, 42 days old, 20.6-29.2 g	Diet	13	0, 30, 120, 480	No treatment related effects on mortality, clinical signs, organ weight or gross and microscopic pathology. Food consumption decreased in weeks 1-2 for males and weeks 1-7 for females, but not in dose-dependent manner. Reductions in body weight gain in all groups (12-14% for high dose group). Increased water consumption in 30 mg/kg group. <u>Laboratory</u> : treatment-related increases in alkaline phosphatase levels in high dose males, liver glycogen values decreased in all treated males and mid and high dose females.
Rat Chbb:Thom  20M, 20F/group, 150-180 g females; 180- 250 g males	Diet	13, 6 week recovery groups after 13 weeks treatment (10 animals/ group)	0, 30, 60, 120, 240	No treatment related effects on mortality, water consumption, ophthalmology, heart rates, hematology, fecal occult blood, gross pathology, organ weights, histopathology or bone marrow cytology. <u>Clinical Signs</u> : Unkempt appearance during first 2 weeks of treatment for 120 and 240 mg/kg groups.

Species/Strain Initial Group	Dosing Method	Duration of Treatment (w)	Dose (mg/kg/day)	Results
				<p>Food consumption slightly decreased in males (all groups) and high dose females; decreases in body weight gains greatest in high dose group; increase in liver weights for females and heart weights (high dose females).</p> <p><u>Laboratory:</u> Treatment-related increases in alkaline phosphatase in two high dose groups (reversible); decreased GPT, decreased leucine arylamidase (females only), liver glycogen (high dose grps only), increased total cholesterol (females) and increased amylase (females, two high doses). All lab changes were reversible and generally not statistically significant.</p> <p><u>Conclusions:</u> 120 mg probably the MTD.</p>
<b>Chronic Toxicity</b>				
Rat Sprague-Dawley  25M, 25F/group; 4 weeks old at receipt	Diet	52	0, 2, 16, 120 in lactose	<p>No treatment-related effects on mortality, clinical signs, food consumption, water consumption, ophthalmoscopy, hematology, urinalysis, organ weights or gross or microscopic pathology.</p> <p><u>Body weight gains</u> decreased by 15% for the high dose animals.</p> <p><u>Laboratory:</u> Alkaline phosphatase values increased at weeks 26 and 52 in high dose animals.</p> <p><u>Conclusions:</u> MTD is 120 mg/kg/day.</p>
Dog Chbb:Beagle  4M, 4F/group; age 11-18 months, weight 9.1-13.6 kg	Capsule	52	0, 0.05, 2, 50	<p>No treatment-related effects on body weights, food consumption, heart rate, ECGs, blood pressure, ophthalmoscopy, hematology, bone marrow cytology, urinalysis and gross pathology.</p> <p><u>Clinical Signs:</u> Clonic tonic spasms in mid and high dose groups eliminated with glucose injection. Two deaths possibly due to seizures in high dose groups. Decreased prostate weight in 50 mg males, enlarged periportal areas in liver in some high dose animals.</p> <p><u>Laboratory:</u> Reduced glucose concentrations up to 60%, increased liver enzymes and amylase in some high dose animals.</p> <p><u>Conclusions:</u> NOEL: 0.05 mg/kg.</p>

**Table 12 – Carcinogenicity**

Species/ Strain Initial Group	Dosing Method	Duration of Treatment (w)	Dose (mg/kg/day)	Results
Mouse CD-1  50M, 50F	Diet	104	0, 50, 170, 500	<p><u>Deaths:</u> 271 premature deaths. High dose males showed a slight increase in mortality compared with controls.</p> <p><u>Clinical Signs:</u> Body weight reductions up to 11% observed at 170 and 500 mg doses.</p> <p><u>Tumours/Lesions:</u> No evidence of tumorigenic potential, no indication of non-neoplastic toxic effects.</p> <p><u>Conclusions:</u> No carcinogenic potential.</p>
Rat Chbb:Thom  50M, 50F	Diet	104	0, 15, 30, 60, 120	<p><u>Deaths:</u> 184 died or were sacrificed prematurely (83 M, 101 F). A dose-related decrease in mortality compared to controls was apparent in males given 60 or 120 mg/kg.</p> <p><u>Clinical Signs:</u> No signs of tumorigenic effect up to 30 mg/kg, and no evidence of non-neoplastic toxic effects.</p> <p><u>Tumors/Lesions:</u> Slight increase in incidence of benign thyroid and liver tumors observed at 60 and/or 120 mg/kg. Thyroid, follicular cell adenomas increased in males but not females; Hepatocellular adenomas increased in males at 120 mg/kg but no progression to malignant carcinomas; Females had increased incidence of non-neoplastic hepatocellular metaplasia of the pancreas at all dose levels and males at 60 and 120 mg/kg.</p> <p><u>Conclusions:</u> NOEL: 30 mg/kg for males and females.</p>

**Table 13 - Reproduction and Teratology**

Species/ Strain Initial Group	Dosing Method	Duration of Treatment	Dose (mg/kg/day)	Results
<b>Fertility Studies - Segment I Studies</b>				
Rat, Chbb:Thom  FO:24M, 24F F1: 1M, 1F per litter	Gavage	FO:PND22  F1:GD14 to 16	M-O: 1, 30, 300 F-O: 1, 30, 80 -Dosing prior to breeding and continued for females throughout lactation.  F <sub>0</sub> Dosing: M= + 10 w to mating F= +2 w to GD22	<u>Parental Effects:</u> Decreased body weight gain (males and females high dose groups). No effect on reproduction or fertility. High dose females had decreased corpora lutea and implantation sites, increased resorptions, decrease in live births and decreased fetal survival. <u>Offspring Effects:</u> Abnormal limb development resulting in abnormal gait. <u>Conclusions (NOEL):</u> F <sub>0</sub> : M: 1 mg/kg; F: 30 mg/kg; F <sub>1</sub> : M:<1 mg/kg; F: 1mg/kg
<b>Embryo Toxicity Studies - Segment II</b>				
Rat, Chbb:Thom  36F (pregnant)	Gavage	Day 7-16; Some rats sacrificed on G22. The remainder allowed to naturally deliver their pups.	0, 0.5, 5, 80	<u>Maternal Effects:</u> Significant decrease in body weight gain and food consumption (high dose) and slightly decreased at 5 mg/kg dose; For GD22 sacrificed rats there was an increase in the no. of total and early resorptions and post-implantation loss in the high dose group. <u>Offspring Effects:</u> No malformations; however, dose dependent ossification delays and decrease in post-weaning body weight gain in male offspring at two highest doses. <u>Conclusions (NOEL):</u> F: 0.5 mg/kg; Embryo/fetal: 0.5 mg/kg
Rabbit Chbb:HM  21F (pregnant)	Gavage	Day 6-18; Dams sacrificed on GD 29	0, 0.1, 0.25, 0.9	<u>Maternal Effects:</u> Increase in food consumption and body weight gain in mid and high dose groups; increased incidence in abortion and resorptions in high dose group. <u>Offspring Effects:</u> Higher incidence of skeletal malformations and variations in the high dose group. <u>Conclusions (NOEL):</u> F: 0.1 mg/kg; Embryo/fetal: 0.1 mg/kg
<b>Peri-postnatal Toxicity Studies - Segment III</b>				
Rat, Chbb:Thom  23F (pregnant) 4F (pregnant- for milk analysis)	Gavage	Day 16 PC up to day 22 PP; cross-fostering group also included	0, 0.5, 5, 30, 80	<u>Maternal Effects:</u> Decrease in body weight gain for two high dose groups. <u>Offspring Effects:</u> Dose-dependent increase in postnatal mortality, reduced body weight gain, abnormal limb development in two high dose groups and delay in vaginal opening for three high dose groups. Cross-fostered offspring also demonstrated

Species/ Strain Initial Group	Dosing Method	Duration of Treatment	Dose (mg/kg/day)	Results
control and high dose				abnormal limb development. Reduction in the reproductive capacity of offspring in low dose groups; mid dose groups unaffected, however corpora lutea, implantation sites and viable fetuses were affected at 5 mg/kg or higher. <u>Conclusions (NOEL):</u> F: 5 mg/kg; Embryo/fetus: <0.5 mg/kg
Rat Chbb:Thom  13F (pregnant)	Gavage	<u>Dosing Windows:</u> GD 1 to 5 GD 6 to 16 GD 17 to 22 PND 1 to 14 PND 15 to 21	80 (5 treatment window groups)	<u>Offspring Effects:</u> No developmental impairment during embryogenesis and early fetogenesis. Long bone deformities not evident if treatment limited to first 2 trimesters (GD 1-16). <u>Conclusions:</u> Critical time point appears to be late gestation and/or were more pronounced in early lactation.
Rat, Chbb:Thom  25F (pregnant)	Gavage	<u>Dosing Windows:</u> GD 7 to 22 PN 1 to 21  Bone x-ray analyses performed postpartum weeks 4, 6 and 10.	0, 80	<u>Offspring Effects:</u> Moderate to severe bone deformities at postnatal week 4, gradually dissipating by week 10. Lactational exposure produced a persistent moderate to severe deformation in the bones. X-ray confirmed chondromalacia and inhibited ingrowth of osteogenic buds. <u>Conclusions:</u> Impairment of chondrogenesis due to pharmacodynamic effect.
Rat, Chbb:Thom  6F (pregnant)	Gavage	GD7 to PND7	0, 80 80+ 10% glucose water 80+streptozotocin	Expected limb deformity observed; evaluation of glucose levels showed statistically lower values in the treated females, but animals with the glucose supplement showed no decreases.
Rat, Chbb:Thom  32F (pregnant)	Gavage	<u>Dosing Windows:</u> GD 17-22 (G2) PP 1-14 (G3) GD 17-PP 14 (G4)	0 or 80	<u>Maternal Effects:</u> High mortality in G3 dams during the first 4 days post-delivery. Clinical signs in G2 and G4 dams were related to severe hypoglycemia, decreases in blood glucose levels in treated dams during gestation only. <u>Offspring Effects:</u> Decreases in blood glucose levels in G3 and G4 offspring. X-ray analyses confirmed skeletal deformities in 40% of G2 and 100% of the G3 and G4 offspring. <u>Conclusions:</u> Repaglinide transmitted to milk.

Repaglinide was not teratogenic in rats and rabbits at doses 40 times (rats) and approximately 0.8 times (rabbit) the maximum recommended human dose (on a mg/m<sup>2</sup> basis) throughout pregnancy. However, in some studies in rats, offspring of dams exposed to high levels of repaglinide during the last trimester of pregnancy and during lactation developed skeletal deformities consisting of shortening, thickening and bending of the humerus during the postnatal

period. This effect was not seen at doses up to 2.5 times the maximum recommended human dose (on a  $\text{mg}/\text{m}^2$  basis) throughout pregnancy or at higher doses given during the first two trimesters of pregnancy.

Since animal reproduction studies are not always predictive of human response, GlucoNorm<sup>®</sup> is not recommended for use during pregnancy.

## REFERENCES

1. Ampudia-Blasco FJ, Heinemann L, Bender R et al. Comparative dose-related time-action profiles of glibenclamide and a new non-sulphonylurea drug, AG-EE 623 ZW, during euglycaemic clamp in healthy subjects. *Diabetologia* 1994; 37: 703-707.
2. Kajosaari L.I., Niemi M, Neuvonen M, Laitila J, Neuvonen P.J., Backman J.T. *Clinical Pharmacology and Therapeutics* 2006; 78 (4): 388-399.
3. Wolffenbittel BHR, Nijst L, Sels JPJE, Menheere PPCA, Muller PG. Effects of a new oral hypoglycemic agent, repaglinide, on metabolic control in sulphonylurea-treated patients with NIDDM. *Eur J Clin Pharmacol* 1993; 45: 113-116.
4. Expert Committee of the Canadian Diabetes Advisory Board. Clinical practice guidelines for treatment of diabetes mellitus. *Can Med Assoc J* 1992;147:697-712.
5. Raskin P, McGill J, Hale P, Khutoryansky N, Santiago, O. Repaglinide/Rosiglitazone Combination Therapy of Type 2 Diabetes. *DIABETES, Abstracts from ADA 61<sup>st</sup> Scientific Sessions, June 2001, Vol 50, Supp 2*
6. Marbury T, Ruckle JL, Hatorp P et al. Pharmacokinetics of repaglinide in subjects with renal impairment. *Clinical Pharmacology and Therapeutics* 2000; 67(1): 7-15.
7. Bidstrup TB, Damkier P, Olsen AK, Ekblom M, Karlsson A, Brøsen K. The impact of CYP2C8 polymorphism and grapefruit juice on the pharmacokinetics of repaglinide. *Br J Clin Pharmacol* 2006; 61(1):49-57.
8. Kalliokoski A, Neuvonen M, Neuvonen PJ, Niemi M. Different effects of SLCO1B1 polymorphism on the pharmacokinetics and pharmacodynamics of repaglinide and nateglinide. *J Clin Pharmacol* 2008; 48(3):311-321.
9. Kalliokoski A, Backman JT, Kurkinen KJ, Neuvonen PJ, Niemi M. Effects of Gemfibrozil and Atorvastatin on the Pharmacokinetics of Repaglinide in Relation to SLCO1B1 Polymorphism. *Clin Pharmacol Ther* 2008;doi: 10.1038/clpt.2008.74.
10. Niemi M, Backman JT, Kajosaari LI et al. Polymorphic organic anion transporting polypeptide 1B1 is a major determinant of repaglinide pharmacokinetics. *Clin Pharmacol Ther* 2005; 77(6):468-478.
11. Niemi M, Leathart JB, Neuvonen M, Backman JT, Daly AK, Neuvonen PJ. Polymorphism in CYP2C8 is associated with reduced plasma concentrations of repaglinide. *Clin Pharmacol Ther* 2003; 74(4):380-387.
12. Tirona RG, Leake BF, Merino G, Kim RB. Polymorphisms in OATP-C. Identification of multiple allelic variants associated with altered transport activity among European- and African-Americans. *Journal of Biological Chemistry* 2001; 276(38):35669-35675.

13. Dai D, Zeldin DC, Blaisdell JA et al. Polymorphisms in human CYP2C8 decrease metabolism of the anticancer drug paclitaxel and arachidonic acid. *Pharmacogenetics* 2001; 11(7):597-607.
14. Bahadur N, Leathart JBS, Mutch E et al. CYP2C8 polymorphisms in Caucasians and their relationship with paclitaxel 6alpha-hydroxylase activity in human liver microsomes. *Biochemical Pharmacology* 2002; 64(11):1579-1589.
15. Lecointre, K, Furlan V, Taburet A.M. In vitro effects of tacrolimus on human cytochrome P450. *Fundamental & Clinical Pharmacology* 2002; 455-460
16. Niwa T, Yamamoto S, Saito M, Shiraga T, Takagi A. Effect of Cyclosporine and Tacrolimus on Cytochrome P450 Activities in Human Liver Microsomes. *The Pharmaceutical Society of Japan* 2007; 127(1): 209-216
17. Turk T., Pietruck F., Dolff S., Kriben A., Janseen O.E., Mann K., Philipp T., Heemann U. and Witzke O. Repaglinide in the Management of New-Onset Diabetes Mellitus After Renal Transplantation. *American journal of Transplantation* 2006; 6: 842-846
18. Hatorp V. and Thomsen MS. Drug interaction studies with repaglinide on digoxin or theophylline pharmacokinetics and cimetidine on repaglinide pharmacokinetics. *J. Clin. Pharmacol.* 2002; 40; 184
19. Hatorp V., Hansen Kristian T. and Thomsen M.S. Influence of Drugs Interacting with CYP3A4 on the Pharmacokinetics, Pharmacodynamics, and Safety of the Prandial Glucose Regulator Repaglinide. *J. Clin. Pharmacol.* 2003; 43;649
20. Rosenberg M.A., Strange P., Chohen A. Assessment of pharmacokinetic and pharmacodynamic interactions between warfarin and repaglinide [abstract]. *Diabetes* 48 suppl. 1:A356, 1999.

## Important: Please Read

### PART III: CONSUMER INFORMATION

**GlucNorm® 0.5 mg, 1 mg and 2 mg**  
Repaglinide Tablets  
Oral anti-diabetic agent

Read this carefully before you start taking GlucNorm® and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about GlucNorm®.

#### ABOUT THIS MEDICATION

##### What is GlucNorm® used for:

- To lower blood sugar in patients with type 2 diabetes mellitus whose blood sugar levels cannot be controlled by diet and exercise alone (monotherapy).
- In combination with metformin to lower blood sugar in patients whose blood sugar levels cannot be controlled by diet and exercise only plus metformin alone.
- In combination with rosiglitazone in patients who cannot take metformin and whose blood sugar levels cannot be controlled by diet and exercise plus GlucNorm® or rosiglitazone alone.

##### How does GlucNorm® work?

GlucNorm® is an oral anti-diabetic agent used for the treatment of diabetes mellitus. It helps your body release more insulin when your blood sugar is high. This helps improve your blood sugar control.

##### What are the ingredients in GlucNorm®?

Medicinal ingredient: Repaglinide

Nonmedicinal ingredients: Amberlite (polacrillin potassium), calcium hydrogen phosphate, glycerol, magnesium stearate, maize starch, meglumine, microcrystalline cellulose, poloxamer (0.5 mg), povidone (polyvidone), red iron oxide (2 mg), yellow iron oxide (1 mg).

##### GlucNorm® comes in the following dosage forms:

GlucNorm® is available in three strengths in bottles of 100 tablets:

- 0.5 mg (white tablets)
- 1 mg (yellow tablets)
- 2 mg (peach-coloured tablets)

##### Do not use GlucNorm® if you:

- Have a known hypersensitivity to repaglinide tablets or any of the other ingredients in GlucNorm®.
- Have diabetic ketoacidosis (accumulation of ketones in the blood and urine).
- Have type 1 diabetes.
- Have severe liver disease.
- Are taking gemfibrozil (a medicine used to lower increased fat levels in the blood).
- Are taking clopidogrel (a medicine used to prevent blood clots).

#### WARNINGS AND PRECAUTIONS

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take GlucNorm®. Talk about any health conditions or problems you may have, including if you:

- Have a history of allergy or intolerance to any medications or other substances
- Have a history of liver or kidney problems
- Are or think you may be pregnant
- Are breastfeeding
- Are over 75 years of age

**Other warnings you should know about:**

GlucoNorm<sup>®</sup> is not recommended for use in children and adolescents less than 18 years of age.

The treatment with insulin secretagogues (drugs that stimulate insulin secretion from the pancreas) in general has been associated with more heart-related deaths as compared to treatment with diet alone or diet plus insulin.

GlucoNorm<sup>®</sup> may cause low blood sugar (hypoglycemia), especially if you miss a meal, exercise for a long time, drink alcohol or use another anti-diabetic medication with GlucoNorm<sup>®</sup>.

You should ask your doctor or pharmacist or diabetes educator about symptoms of low blood sugar and what to do if you experience these symptoms. You should also test your blood sugar as instructed by your doctor.

The warnings signs of hypoglycemia may come on suddenly and can include:

- cold sweat
- cool pale skin
- headache
- rapid heartbeat
- feeling sick
- difficulty in concentrating

Severe hypoglycemia can cause loss of consciousness, seizure, brain damage and even death.

Your blood sugar may get too high (hyperglycemia) if you have fever, infection, surgery or trauma (stress conditions). In such cases, contact your doctor as your medication may need to be adjusted.

**Driving and Operating Machinery:**

Alertness and reactions may be impaired due to low blood sugar (hypoglycemia), especially when beginning or after changing treatment or when GlucoNorm<sup>®</sup> is not taken regularly. This may affect your ability to drive or to operate machinery.

**INTERACTIONS WITH THIS MEDICATION**

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**Serious Drug Interactions**

Do not use GlucoNorm<sup>®</sup> (repaglinide) with gemfibrozil (used to treat high blood fats).

Do not use GlucoNorm<sup>®</sup> (repaglinide) with clopidogrel (a medicine used to prevent blood clots).

Many medicines affect the way glucose works in your body and this may influence your GlucoNorm<sup>®</sup> dose. Listed below are the most common medicines which may affect your treatment with GlucoNorm<sup>®</sup>:

- Other anti-diabetic agents (used to lower blood sugar)
- Monoamine oxidase inhibitors (used to treat depression)
- Beta-blocking agents (used to treat high blood pressure and certain heart conditions)

- Angiotensin converting enzyme (ACE) inhibitors (used to treat high blood pressure and certain heart conditions)
- Salicylates (e.g. acetylsalicylic acid)
- Octreotide
- Non-steroidal anti-inflammatory agents (NSAIDs) (a type of painkillers)
- Anabolic steroids and corticosteroids (used for anemia or to treat inflammation)
- Oral contraceptives (used for birth control)
- Thiazides (diuretics or 'water pills')
- Danazol (used to treat breast cysts and endometriosis)
- Thyroid hormones (used to treat patients with low levels of thyroid hormones)
- Sympathomimetics (used to treat asthma)
- Clarithromycin, trimethoprim, rifampicin (antibiotics)
- Itraconazole, ketoconazole (anti-fungal drug)
- Phenytoin, carbamazepine, phenobarbital (used to treat epilepsy/seizures)
- Cyclosporine (used to suppress the immune system)
- Deferasirox (used to reduce chronic iron overload)
- Non-prescription and over the counter drugs such as drugs for appetite control, asthma, colds, cough, hay fever or sinus problems

Alcohol may increase the effect of GlucoNorm<sup>®</sup> on lowering your blood sugar and therefore impair your ability to concentrate. Avoid drinking alcohol while you are taking GlucoNorm<sup>®</sup>.

Grapefruit juice may increase the effect of GlucoNorm<sup>®</sup>.

## PROPER USE OF THIS MEDICATION

### How to take GlucoNorm<sup>®</sup>:

Your doctor will prescribe GlucoNorm<sup>®</sup> according to your needs. Take GlucoNorm<sup>®</sup> exactly as prescribed by your doctor.

### Usual dose:

GlucoNorm<sup>®</sup> tablets should be taken with meals, usually 15 minutes before the meal. However, GlucoNorm<sup>®</sup> tablets may be taken 30 minutes before a meal or right before a meal.

### Overdose:

If you take more GlucoNorm<sup>®</sup> than you should, your blood sugar may become too low leading to a hypoglycemic event. The symptoms of such an event include: headache, dizziness, tiredness, rapid heartbeat, nervousness, shakiness, nausea and sweating.

Discuss with your healthcare professional about how to treat low blood sugar.

If you think you have taken too much GlucoNorm<sup>®</sup>, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

### Missed Dose

If you miss a dose of GlucoNorm<sup>®</sup>, do not take the missed dose. Wait and take your usual dose before your next meal.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

**What are the possible side effects from using GlucoNorm®?**

These are not all the possible side effects you may feel when taking GlucoNorm®. If you experience any side effects not listed here, contact your healthcare professional. Please also see WARNINGS AND PRECAUTIONS.

The following side effects may occur during your treatment with GlucoNorm®:

**Common**

- Visual disturbance
- Abdominal pain
- Nausea
- Constipation

**Uncommon**

- Liver dysfunction
- Itching
- Redness
- Vomiting
- Rash
- Hives
- Abnormal blood test results

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	<b>Low blood sugar</b> (hypoglycemia)  Symptoms include: cold sweat, cool pale skin, headache, rapid heartbeat, feeling sick and/or difficulty in concentrating.		✓	
	<b>High blood sugar</b> (hyperglycemia)  Symptoms include: increased urination, feeling thirsty, dry skin and dry mouth.		✓	
Common	Sudden severe headache or worsening of headache, dizziness, tremors, fatigue or increased sweating			✓
	Diarrhea, constipation, gas, upset stomach, nausea or abdominal pain		✓	
	Sudden partial or complete loss of vision			✓
Uncommon	Chest pain or pressure, and/or shortness of breath			✓

## SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
<b>Allergy</b> Symptoms include: swelling, difficulty breathing, rapid heartbeat, feeling dizzy and sweating			✓

If you have troublesome symptom or side effects that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

## REPORTING SUSPECTED SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

### 3 ways to report:

- Online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- By calling 1-866-234-2345 (toll-free)
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program  
Health Canada, Postal Locator 0701E  
Ottawa, ON  
K1A 0K9

Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

## HOW TO STORE IT

### Storage:

Keep out of reach and sight of children.

GlucNorm® should be stored between 15°C - 25°C, which is generally room temperature. Do not store GlucNorm® in moist areas, like the bathroom medication cabinet or other damp places. Always store it in the bottle it came in, with the lid on tight.

Do not use GlucNorm® after the expiry date on the package.

Medicines should not be disposed of down the drain or in household garbage. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

## MORE INFORMATION

If you want more information about GlucoNorm®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professional and includes this Patient Medication Information by visiting the Health Canada website at <http://www.hc-sc.gc.ca>; or by calling Novo Nordisk Canada Inc. at 1-800-465-4334.

The leaflet was prepared by Novo Nordisk Canada Inc.

Manufactured by:

For more information contact:  
Novo Nordisk Canada Inc.  
Mississauga, Ontario, Canada  
L4W 5L6

**1 • 800 • 465 • 4334**

[www.novonordisk.ca](http://www.novonordisk.ca)

Last revised: June 2015