Tablets for Oral Use.

Pharmacist Information:
Dispense in tight, light-resistant container with child resistant closure as defined in USP.

Protect from moisture.

Keep bottles tightly closed.

Keep this and all drugs out of the reach of children.

Store at 20° to 25°C (68° to 77°F); [See USP Controlled Room Temperature].

Each tablet contains:
Repaglinide, USP.....1 mg

C.S.No. 5459L71
Iss. 3/09

NDC 57664-745-88

Repaglinide Tablets, USP

1 mg

Rx Only

100 Tablets

Distributed by:

CARACO
PHARMACEUTICAL LABORATORIES, LTD.
Detroit, MI 48202

Usual Dosage:
See package outsert for complete product information.

S.S.No. 6464L01

LOT NO.:

EXP. DATE:

Tablets for Oral Use.

Pharmacist Information:
Dispense in tight, light-resistant container with child resistant closure as defined in USP.

Protect from moisture.

Keep bottles tightly closed.

Keep this and all drugs out of the reach of children.

Store at 20° to 25°C (68° to 77°F); [See USP Controlled Room Temperature].

Each tablet contains:
Repaglinide, USP.....1 mg

C.S.No. 5460L71
Iss. 3/09

NDC 57664-745-13

Repaglinide Tablets, USP

1 mg

Rx Only

500 Tablets

Distributed by:

CARACO
PHARMACEUTICAL LABORATORIES, LTD.
Detroit, MI 48202

Usual Dosage:
See package outsert for complete product information.

S.S.No. 6465L01

LOT NO.:

EXP. DATE:

Tablets for Oral Use.

Pharmacist Information:
Dispense in tight, light-resistant container with child resistant closure as defined in USP.

Protect from moisture.

Keep bottles tightly closed.

Keep this and all drugs out of the reach of children.

Store at 20° to 25°C (68° to 77°F); [See USP Controlled Room Temperature].

Each tablet contains:
Repaglinide, USP.....1 mg

C.S.No. 5461L71
Iss. 3/09

NDC 57664-745-18

Repaglinide Tablets, USP

1 mg

Rx Only

1000 Tablets

Distributed by:

CARACO
PHARMACEUTICAL LABORATORIES, LTD.
Detroit, MI 48202

Usual Dosage:
See package outsert for complete product information.

S.S.No. 6466L01

LOT NO.:
EXP. DATE:

Tablets for Oral Use.

Pharmacist Information:
Dispense in tight, light-resistant container with child resistant closure as defined in USP.

Protect from moisture.

Keep bottles tightly closed.

Keep this and all drugs out of the reach of children.

Store at 20° to 25°C (68° to 77°F); [See USP Controlled Room Temperature].

Each tablet contains:
Repaglinide, USP.....2 mg

C.S.No. 5462L71
Iss. 3/09

NDC 57664-747-88

Repaglinide Tablets, USP

2 mg

Rx Only

100 Tablets

Distributed by:

CARACO
PHARMACEUTICAL LABORATORIES, LTD.
Detroit, MI 48202

Usual Dosage:
See package outsert for complete product information.

S.S.No. 6467L01

LOT NO.:

EXP. DATE:

Tablets for Oral Use.

Pharmacist Information:
Dispense in tight, light-resistant container with child resistant closure as defined in USP.

Protect from moisture.

Keep bottles tightly closed.

Keep this and all drugs out of the reach of children.

Store at 20° to 25°C (68° to 77°F); [See USP Controlled Room Temperature].

Each tablet contains:
Repaglinide, USP.....2 mg

C.S.No. 5463L71
Iss. 3/09

NDC 57664-747-13

Repaglinide Tablets, USP

2 mg

Rx Only

500 Tablets

Distributed by:

CARACO
PHARMACEUTICAL LABORATORIES, LTD.
Detroit, MI 48202

Usual Dosage:
See package outsert for complete product information.

S.S.No. 6468L01

N 3 57664 74713 1

LOT NO.:

EXP. DATE:

Tablets for Oral Use.

Pharmacist Information:
Dispense in tight, light-resistant container with child resistant closure as defined in USP.

Protect from moisture.

Keep bottles tightly closed.

Keep this and all drugs out of the reach of children.

Store at 20° to 25°C (68° to 77°F); [See USP Controlled Room Temperature].

Each tablet contains:
Repaglinide, USP.....2 mg

C.S.No. 5464L71
Iss. 3/09

NDC 57664-747-18

Repaglinide Tablets, USP

2 mg

Rx Only

1000 Tablets

Distributed by:

CARACO
PHARMACEUTICAL LABORATORIES, LTD.
Detroit, MI 48202

Usual Dosage:
See package outsert for complete product information.

S.S.No. 6469L01

LOT NO.:

EXP. DATE:

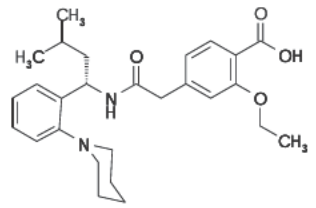
REPAGLINIDE TABLETS, USP
1 mg and 2 mg

Rx only

DESCRIPTION

Repaglinide is an oral blood glucose-lowering drug of he meglitinide class used in the management of type 2 diabetes mellitus (also known as non-insulin dependent diabetes mellitus or NIDDM). Repaglinide, S(+)2-ethoxy-4(2((3-me hyl-1-(2-(1-piperidinyl) phenyl)- butyl) amino)-2 oxoethyl) benzoic acid, is chemically unrelated to he oral sulfonylurea insulin secretagogues.

The structural formula is as shown below:



Repaglinide is a white to off-white powder with molecular formula $C_{27}H_{36}N_2O_4$ and a molecular weight of 452.6. Repaglinide tablets contain 1 mg or 2 mg of repaglinide. In addition each tablet contains the following inactive ingredients: dicalcium phosphate (anhyd ous), mic ocrystalline cellulose, co n starch, meglumine, c oscarmellose sodium, povidone, poloxamer, magnesium stearate, and colloidal silicon dioxide. The 1 mg and 2 mg tablets contain i on oxides (yellow and red, respectively) as coloring agents.

CLINICAL PHARMACOLOGY

Mechanism of Action

Repaglinide lowers blood glucose levels by stimulating the release of insulin f om he pancreas. This action is dependent upon functioning beta (β) cells in the pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations.

Repaglinide closes ATP-dependent potassium channels in he β-cell membrane by binding at characterizable sites. This potassium channel blockade depolarizes he β-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 f om he gast ointestinal tract. After single and multiple oral doses in healthy subjects or in patients, peak plasma drug levels (C_{max}) occur within 1 hour (T_{max}). Repaglinide is rapidly eliminated f om the blood stream wi h a half-life of app oximately 1 hour. The mean absolute bioavailability is 56%. When repaglinide was given wi h food, he mean T_{max} was not changed, but the mean C_{max} and AUC (area under he time/plasma concentration curve) were decreased 20% and 12.4%, respectively.

Distribution: After intravenous (IV) dosing in heal hy subjects, he volume of distribution at steady state (V_{ss}) was 31 L, and the total body clearance (CL) was 38 L/h. P otein binding and binding to human serum albumin was greater han 98%.

Metabolism: Repaglinide is completely metabolized by oxidative biotransformation and direct conjugation wi h glucu onic acid after ei her an IV or oral dose. The major metabolites are an oxidized dicarboxylic acid (M2), the a omatic amine (M1), and the acyl glucu onide (M7). The cytoch ome P-450 enzyme system, specifically 2C8 and 3A4, have been shown to be involved in the N-dealkylation of repaglinide to M2 and he further oxidation to M1. Metabolites do not contribute to he glucose-lowering effect of repaglinide.

Repaglinide appears to be a substrate for active hepatic uptake transporter (organic anion transporting p otein OATP1B1).

Excretion: Wi hin 96 hours after dosing with ^{14}C-repaglinide as a single, oral dose, app oximately 90% of he radiolabel was recovered in he feces and app oximately 8% in he urine. Only 0.1% of the dose is cleared in he urine as parent compound. The major metabolite (M2) accounted for 60% of he administered dose. Less han 2% of parent drug was recovered in feces.

Pharmacokinetic Parameters: The pharmacokinetic parameters of repaglinide obtained f om a single-dose, c ossover study in heal hy subjects and f om a multiple-dose, parallel, dose-p oportionality (0.5, 1, 2 and 4 mg) study in patients wi h type 2 diabetes are summarized in the following table:

Parameter	Patients with type 2 diabetes[a]
Dose 0.5 mg 1 mg 2 mg 4 mg	$AUC_{0\text{-}24\ hr}$ Mean ± SD (ng/mL*hr): 68.9 ± 154.4 125.8 ± 129.8 152.4 ± 89.6 447.4 ± 211.3
Dose 0.5 mg 1 mg 2 mg 4 mg	$C_{max\ 0\text{-}5\ hr}$ Mean ±SD (ng/mL): 9.8 ± 10.2 18.3 ± 9.1 26.0 ± 13.0 65.8 ± 30.1
Dose 0.5-4 mg	$T_{max\ 0\text{-}5\ hr}$ Means (SD) 1.0 - 1.4 (0.3 - 0.5) hr
Dose 0.5-4 mg	$T^1/_2$ Means (Ind Range) 1.0 - 1.4 (0.4-8.0) hr
Parameter	Healthy Subjects
CL based on i.v.	38 ± 16 L/hr
V_{ss} based on i.v.	31 ± 12 L
AbsBio	56 ± 9%

a: dosed preprandially wi h hree meals
CL = total body clearance
V_{ss} = volume of distribution at steady state
AbsBio = absolute bioavailability

These data indicate that repaglinide did not accumulate in serum. Clearance of oral epaglinide did not change over he 0.5 - 4 mg dose range, indicating a linear relationship between dose and plasma drug levels.

Variability of Exposure: Repaglinide AUC after multiple doses of 0.25 to 4 mg wi h each meal varies over a wide range. The intra-individual and inter-individual coefficients of variation were 36% and 69%, respectively. AUC over he therapeutic dose range included 69 to 1005 ng/mL*hr, but AUC exposure up to 5417 ng/mL*hr was reached in dose escalation studies wi hout apparent adverse consequences.

Special Populations:

Geriatric: 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 g oup of patients <65 years of age and a comparably sized g oup of patients ≥65 years of age. (See **PRECAUTIONS, Geriatric Use**)

Pediatric: No studies have been performed in pediatric patients.

Gender: A comparison of pharmacokinetics in males and females showed he AUC over he 0.5 mg to 4 mg dose range to be 15% to 70% higher in females wi h type 2 diabetes. This difference was not reflected in he frequency of hypoglycemic episodes (male: 16%; female: 17%) or o her adverse events. Wi h 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 he effects of race have been performed, but in a U.S. 1-year study in patients wi h 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, here was no apparent difference in exposure (AUC) between Caucasians (n=74) and Hispanics (n=33).

Drug-Drug Interactions:

Drug interaction studies performed in heal hy volunteers show hat Repaglinide had no clinically relevant effect on he pharmacokinetic p operties of digoxin, theophylline, or warfarin. Co-administration of cimetidine wi h Repaglinide did not significantly alter the absorption and disposition of repaglinide.

Additionally, he following drugs were studied in heal hy volunteers wi h co-administration of Repaglinide. Listed below are he results:

CYP2C8 and CYP3A4 Inhibitors/Inducer

Gemfibrozil and Itraconazole: Co-administration of gemfib ozil (600 mg) and a single dose of 0.25 mg Repaglinide (after 3 days of twice-daily 600 mg gemfib ozil) resulted in an 8.1-fold higher repaglinide AUC and p olonged repaglinide half-life f om 1.3 to 3.7 hr. Co-administration wi h itraconazole and a single dose of 0.25 mg Repaglinide (on he third day of a regimen of 200 mg initial dose, twice-daily 100 mg itraconazole) resulted in a 1.4-fold higher repaglinide AUC. Co-administration of both gemfib ozil and itraconazole wi h Repaglinide resulted in a 19-fold higher repaglinide AUC and p olonged repaglinide half-life to 6.1 hr. Plasma repaglinide concentration at 7 h increased 28.6-fold with gemfibrozil co-administration and 70.4-fold wi h he gemfibrozil-itraconazole combination (see **CONTRAINDICATIONS, PRECAUTIONS, Drug-Drug Interactions**).

Fenofibrate: Co-administration of 200 mg fenofibrate wi h a single dose of 0.25 mg repaglinide (after 5 days of once daily fenofibrate 200 mg) resulted in unchanged AUC and C_{max} values for bo h drugs.

Ketoconazole: Co-administration of 200 mg ketoconazole and a single dose of 2 mg Repaglinide (after 4 days of once daily ketoconazole 200 mg) resulted in a 15% and 16% increase in repaglinide AUC and C_{max}, respectively. The increases were f om 20.2 ng/mL to 23.5 ng/mL for C_{max} and f om 38.9 ng/mL*hr to 44.9 ng/mL*hr for AUC.

Trimethoprim: Co-administration of 160 mg trime hoprim and a single dose of 0.25 mg repaglinide (after 2 days of twice daily and one dose on the third day of trime hoprim 160 mg) resulted in a 61% and 41% increase in repaglinide AUC and C_{max}, respectively. The increase in AUC was f om 5.9 ng/mL*hr to 9.6 ng/mL*hr and he increase in C_{max} was f om 4.7 ng/mL to 6.6 ng/mL.

Cyclosporine: Co-administration of 100 mg cyclosporine wi h a single dose of 0.25 mg repaglinide (after two 100 mg doses of cyclosporine twelve hours apart) increased the repaglinide (0.25 mg) C_{max} 1.8-fold and he AUC 2.5-fold in an interaction study with heal hy volunteers (see **PRECAUTIONS**, Drug-Drug Interactions).

Rifampin: Co-administration of 600 mg rifampin and a single dose of 4 mg Repaglinide (after 6 days of once daily rifampin 600 mg) resulted in a 32% and 26% decrease in repaglinide AUC and C_{max}, respectively. The decreases were from 40.4 ng/mL to 29.7 ng/mL for C_{max} and from 56.8 ng/mL*hr to 38.7 ng/mL*hr for AUC.

In another study, co-administration of 600 mg rifampin and a single dose of 4 mg Repaglinide (after 6 days of once daily rifampin 600 mg) resulted in a 48% and 17% decrease in repaglinide median AUC and median C_{max} respectively. The median decreases were f om 54 ng/mL*hr to 28 ng/mL*hr for AUC and f om 35 ng/mL to 29 ng/mL for C_{max}. Repaglinide administered by itself (after 7 days of once daily rifampin 600 mg) resulted in an 80% and 79% decrease in repaglinide median AUC and C_{max} respectively. The decreases were f om 54 ng/mL*hr to 11 ng/mL*hr for AUC and f om 35 ng/mL to 7.5 ng/mL for C_{max}.

Levonorgestrel & Ethinyl Estradiol: Co-administration of a combination tablet of 0.15 mg levonorgestrel and 0.03 mg e hinyl estradiol administered once daily for 21 days wi h 2 mg Repaglinide administered three times daily (days 1-4) and a single dose on Day 5 resulted in 20% increases in repaglinide, levonorgestrel, and ethinyl estradiol C_{max}. The increase in repaglinide C_{max} was f om 40.5 ng/mL to 47.4 ng/mL. Ethinyl estradiol AUC parameters were increased by 20%, while repaglinide and levonorgestrel AUC values remained unchanged.

Simvastatin: Co-administration of 20 mg simvastatin and a single dose of 2 mg Repaglinide (after 4 days of once daily simvastatin 20 mg and hree times daily Repaglinide 2 mg) resulted in a 26% increase in repaglinide C_{max} f om 23.6 ng/mL to 29.7 ng/mL. AUC was unchanged.

Nifedipine: Co-administration of 10 mg nifedipine wi h a single dose of 2 mg Repaglinide (after 4 days of three times daily nifedipine 10 mg and three times daily Repaglinide 2 mg) resulted in unchanged AUC and C_{max} values for bo h drugs.

Clarithromycin: Co-administration of 250 mg clari h omycin and a single dose of 0.25 mg Repaglinide (after 4 days of twice daily clari h omycin 250 mg) resulted in a 40% and 67% increase in repaglinide AUC and C_{max}, respectively. The increase in AUC was f om 5.3 ng/mL*hr. to 7.5 ng/mL*hr and he increase in C_{max} was f om 4.4 ng/mL to 7.3 ng/mL.

Deferasirox: Co-administration of deferasi ox (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 cont ol and an increase in C_{max} of 62% (see **PRECAUTIONS, Drug-Drug Interactions**).

Renal Insufficiency: Single-dose and steady-state pharmacokinetics of repaglinide were compared between patients with type 2 diabetes and normal renal function (CrCl > 80 mL/min), mild to moderate renal function impairment (CrCl = 40 - 80 mL/min), and severe renal function impairment (CrCl = 20 – 40 mL/min). Bo h AUC and C_{max} of repaglinide were similar in patients wi h normal and mild to moderately impaired renal function (mean values 56.7 ng/mL*hr vs 57.2 ng/mL*hr and 37.5 ng/mL vs 37.7 ng/mL, respectively.) Patients wi h severely reduced renal function had elevated mean AUC and C_{max} values (98.0 ng/mL*hr and 50.7 ng/mL, respectively), but this study showed only a weak correlation between repaglinide levels and creatinine clearance. Initial dose adjustment does not appear to be necessary for patients wi h mild to moderate renal dysfunction. **However, patients with type 2 diabetes who have severe renal function impairment should initiate Repaglinide therapy with the 0.5 mg dose - subsequently, patients should be carefully titrated. Studies were not conducted in patients with creatinine clearances below 20 mL/min or patients with renal failure requiring hemodialysis.**

Hepatic Insufficiency: A single dose, open-label study was conducted in 12 heal hy subjects and 12 patients wi h ch onic liver disease (CLD) classified by Child-Pugh scale and caffeine clearance. Patients wi h moderate to severe impairment of liver function had higher and more p olonged serum concentrations of bo h total and unbound repaglinide han hea thy subjects ($AUC_{heal\ hy}$: 91.6 ng/mL*hr; $AUC_{C\ D\ pa\ ients}$: 368.9 ng/mL*hr; $C_{max,\ heal\ hy}$: 46.7 ng/mL; $C_{max,\ CLD\ patients}$: 105.4 ng/mL). AUC was statistically correlated wi h caffeine clearance. No difference in glucose p ofiles was observed ac oss patient g oups. Patients wi h impaired liver function may be exposed to higher concentrations of repaglinide and its associated metabolites than would patients wi h normal liver function receiving usual doses. Therefore, **Repaglinide should be used cautiously in patients with impaired liver function. Longer intervals between dose adjustments should be utilized to allow full assessment of response.**

Clinical Trials

Monotherapy Trials

A four-week, double-blind, placebo-cont olled dose response trial was conducted in 138 patients wi h type 2 diabetes using doses ranging f om 0.25 to 4 mg taken with each of three meals. Repaglinide therapy resulted in dose-p oportional 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 wi hin 1-2 weeks.

In a double-blind, placebo-controlled, 3-mon h dose titration study, Repaglinide or placebo doses for each patient were increased weekly f om 0.25 mg h ough 0.5, 1, and 2 mg, to a maximum of 4 mg, until a fasting plasma glucose (FPG) level <160 mg/dL was achieved or the maximum dose reached. The dose hat achieved he targeted cont ol or the maximum dose was continued to end of study. FPG and 2-hour postprandial glucose (PPG) increased in patients receiving placebo and decreased in patients t eated wi h repaglinide. Differences between he repaglinide- and placebo-treated g oups we e –61 mg/dL (FPG) and -104 mg/dL (PPG). The between-g oup change in HbA_{1c}, which reflects long-term glycemic cont ol, was 1.7% units.

Repaglinide vs. Placebo Treatment:
Mean FPG, PPG, and HbA_{1c}
Changes from baseline after 3 months of treatment:

	FPG (mg/dL)		PPG (mg/dL)		HbA_{1c} (%)	
	PL	R	PL	R	PL	R
Baseline	215.3	220.2	245.2	261.7	8.1	8.5
Change from Baseline (at last visit)	30.3	-31.0*	56.5	-47.6*	1.1	-0.6*

FPG = fasting plasma glucose
PPG = post-prandial glucose
PL = placebo (N=33)
R = repaglinide (N=66)
*: p < 0.05 for between g oup difference

Another double-blind, placebo-cont olled 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_{1c} at he end of he study. HbA_{1c} for he Repaglinide-treated g oups (1 and 4 mg g oups combined) at he end of the study was decreased compared to he placebo-treated g oup in previously naïve patients and in patients previously treated wi h ora hypoglycemic agents by 2.1% units and 1.7% units, respectively. In his fixed-dose trial, patients who were naïve to oral hypoglycemic agent herapy and patients in relatively good glycemic cont ol at baseline (HbA_{1c} below 8%) showed greater blood glucose-lowering including a higher frequency of hypoglycemia. Patients who were previously treated and who had baseline $HbA_{1c} \geq 8\%$ reported hypoglycemia at he same rate as patients randomized to placebo. There was no average gain in body weight when patients previously treated wi h oral hypoglycemic agents were switched to Repaglinide. The average weight gain in patients treated wi h Repaglinide and not previously treated with sulfonylurea drugs was 3.3%.

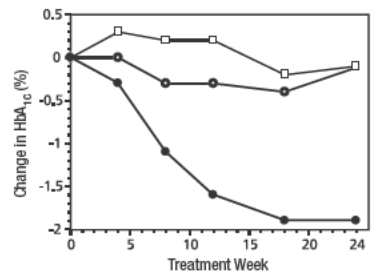
The dosing of Repaglinide relative to meal-related insulin release was studied in hree trials including 58 patients. Glycemic cont ol was maintained during a period in which he meal and dosing patte n was varied (2, 3 or 4 meals per day; before meals x 2, 3, or 4) compared wi h a period of 3 regular meals and 3 doses per day (before meals x 3). It was also shown hat Repaglinide can be administered at the start of a meal, 15 minutes before, or 30 minutes before he meal with the same blood glucose-lowering effect.

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

Combination Trials

A combination therapy regimen of Repaglinide and pioglitazone was compared to mono herapy with ei her agent alone in a 24-week trial hat en olled 246 patients previously treated w th sulfonylurea or metformin monotherapy (HbA_{1c} >7.0%). Numbers of patients treated were: Repaglinide (N = 61), pioglitazone (N = 62), combination (N = 123). Repaglinide dosage was titrated during he first 12 weeks, followed by a 12-week maintenance period. Combination therapy resulted in significantly greater imp ovement in glycemic cont ol as compared to monotherapy (figure below). The changes f om baseline for completers in FPG (mg/dL) and HbA_{1c} (%), respectively were: -39.8 and -0.1 for Repaglinide, -35.3 and -0.1 for pioglitazone and -92.4 and -1.9 for the combination. In his study where pioglitazone dosage was kept constant, he combination herapy g oup showed dose-sparing effects wi h respect to Repaglinide (see figure legend). The greater efficacy esponse of he combination g oup was achieved at a lower daily repaglinide dosage than in he Repaglinide monotherapy g oup. Mean weight increases associated with combination, Repaglinide and pioglitazone therapy were 5.5 kg, 0.3 kg, and 2.0 kg respectively.

HbA_{1c} Values from Repaglinide/Pioglitazone Combination Study
Repaglinide+Pioglitazone Repaglinide Pioglitazone



HbA_{1c} values by study week for patients who completed study (combination, N = 101; Repaglinide, N = 35, pioglitazone, N = 26).

Subjects with FPG above 270 mg/dL were wi hdrawn f om he study.

Pioglitazone dose: fixed at 30 mg/day; Repaglinide median final dose: 6 mg/day for combination and 10 mg/day for mono herapy.

A combination herapy regimen of Repaglinide and osiglitazone was compared to mono herapy w th ei her agent alone in a 24-week trial that en olled 252 patients previously treated w th sulfonylurea or metformin (HbA_{1c} >7.0%). Combination therapy resulted in significantly greater imp ovement in glycemic cont ol as compared to monotherapy (table below). The glycemic effects of the combination therapy were dose-sparing wi h respect to both total daily Repaglinide dosage and total daily osiglitazone dosage (see table legend). A greater efficacy response of the combination herapy g oup was achieved wi h half he median daily dose of Repaglinide and osiglitazone, as compared to he respective mono herapy g oups. Mean weight change associated wi h combination therapy was greater han that of Repaglinide mono herapy.

Mean Changes from Baseline in Glycemic Parameters and Weight in a 24-Week Repaglinide / Rosiglitazone Combination Study[1]

	Repaglinide	Combination	Rosiglitazone
N	63	127	62
HbA_{1c} (%)			
Baseline	9.3	9.1	9.0
Change by 24 weeks	-0.17	-1.43*	-0.56
FPG (mg/dL)			
Baseline	269	257	252
Change by 24 weeks	-54	-94*	-67
Change in Weight (kg)	+1.3	+4.5#	+3.3

[1]: based on intent-to-treat analysis
*: p-value ≤ 0.001 for comparison to either mono herapy
#: p-value < 0.001 for comparison to Repaglinide

Final median doses: osiglitazone - 4 mg/day for combination and 8 mg/day for mono herapy; Repaglinide - 6 mg/day for combination and 12 mg/day for mono herapy

INDICATIONS AND USAGE

Repaglinide is indicated as an adjunct to diet and exercise to imp ove glycemic cont ol in adults with type 2 diabetes mellitus.

CONTRAINDICATIONS

Repaglinide is contraindicated in patients wi h:

1. Diabetic ketoacidosis, with or without coma. This condition should be treated wi h insulin.
2. Type 1 diabetes.
3. Co-administration of gemfib ozil.
4. Known hypersensitivity to he drug or its inactive ingredients.

PRECAUTIONS

General: Repaglinide is not indicated for use in combination wi h NPH-insulin (See **ADVERSE REACTIONS, Cardiovascular Events**).

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of mac ovascular risk reduction wi h Repaglinide or any o her anti-diabetic drug.

Hypoglycemia: All oral blood glucose-lowering drugs including repaglinide are capable of p oducing hypoglycemia. P oper patient selection, dosage, and instructions to he patients are important to avoid hypoglycemic episodes. Hepatic insufficiency may cause elevated repaglinide blood levels and may diminish gluconeogenic capacity, both of which increase he risk of serious hypoglycemia. Elderly, debilitated, or malnourished patients, and hose with adrenal, pituitary, hepatic, or severe renal insufficiency may be particularly susceptible to he hypoglycemic action of glucose-lowering drugs.

Hypoglycemia may be difficult to recognize in the elderly and in people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or p olonged exercise, when alcohol is ingested, or when more han one glucose-lowering drug is used.

Repaglinide
Tablets, USP
1 mg and 2 mg
6470T02

The frequency of hypoglycemia is greater in patients wi h type 2 diabetes who have not been previously treated wi h oral blood glucose-lowering drugs (naïve) or whose HbA_{1c} is less han 8%. Repaglinide should be administered with meals to lessen he risk of hypoglycemia.

Loss of control of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of glycemic cont ol may occur. At such times, it may be necessary to discontinue Repaglinide and administer insulin. The effectiveness of any hypoglycemic drug in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to p ogression of the severity of diabetes or to diminished responsiveness to he drug. This phenomenon is known as secondary failure, to distinguish it f om primary failure in which he drug is ineffective in an individual patient when he drug is first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Information for Patients

Patients should be informed of the potential risks and advantages of Repaglinide and of alte native modes of herapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise p ogram, and of regular testing of blood glucose and HbA_{1c}. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development and concomitant administration of o her glucose-lowering drugs should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Patients should be instructed to take Repaglinide before meals (2, 3, or 4 times a day preprandially). Doses are usually taken within 15 minutes of the meal but time may vary f om immediately preceding he meal to as long as 30 minutes before he meal. **Patients who skip a meal (or add an extra meal) should be instructed to skip (or add) a dose for that meal.**

Laboratory Tests

Response to all diabetic herapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels with a goal of decreasing hese levels towards he normal range. During dose adjustment, fasting glucose can be used to determine he therapeutic response. Thereafter, bo h glucose and glycosylated hemoglobin should be monitored. Glycosylated hemoglobin may be especially useful for evaluating long-term glycemic cont ol. Postprandial glucose level testing may be clinically helpful in patients whose pre-meal blood glucose levels are satisfactory but whose overall glycemic cont ol (HbA_{1c}) is inadequate.

Drug-Drug Interactions

In vitro data indicate hat Repaglinide is metabolized by cytoch ome P450 enzymes 2C8 and 3A4. Consequently, repaglinide metabolism may be altered by drugs which influence hese cytoch ome P450 enzyme systems via induction and inhibition. Caution should therefore be used in patients who are on Repaglinide and taking inhibitors and/or inducers of CYP2C8 and CYP3A4. The effect may be very significant if both enzymes are inhibited at he same time resulting in a substantial increase in repaglinide plasma concentrations. Drugs that are known to inhibit CYP3A4 include antifungal agents like ketoconazole, itraconazole, and antibacterial agents like ery h omycin. Drugs hat are known to inhibit CYP2C8 include agents like trimethoprim, gemfib ozil and montelukast. Drugs that induce he CYP3A4 and/or 2C8 enzyme systems include rifampin, barbiturates, and carbamezapine. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions**.

Repaglinide appears to be a substrate for active hepatic uptake transporter (organic anion transporting p otein OATP1B1). Drugs hat inhibit OATP1B1 (e.g., cyclosporine) may likewise have the potential to increase plasma concentrations of repaglinide. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions**.

In vivo data f om a study hat evaluated he co-administration of a cytoch ome P450 enzyme 3A4 inhibitor, clarith omycin, wi h Repaglinide resulted in a clinically significant increase in repaglinide plasma levels. In addition, an increase in repaglinide plasma levels was observed in a study that evaluated he co-administration of Repaglinide wi h trime hoprim, and Repaglinide with deferasi ox, both cytoch ome P450 enzyme 2C8 inhibitors. These increases in repaglinide plasma levels may necessitate a Repaglinide dose adjustment. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions**.

Gemfib ozil significantly increased Repaglinide exposure. Therefore, patients should not take Repaglinide wi h gemfib ozil. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions**, and **CONTRAINDICATIONS**.

The hypoglycemic action of oral blood glucose-lowering agents may be potentiated by certain drugs including nonste oidal anti-inflammatory agents and other drugs that are highly p otein bound, salicylates, sulfonamides, cyclosporine, chloramphenicol, coumarins, p obenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving oral blood glucose-lowering agents, he patient should be observed closely for hypoglycemia. When such drugs are wi hdrawn f om a patient receiving oral blood glucose-lowering agents, he patient should be observed closely for loss of glycemic cont ol.

Certain drugs tend to p oduce hyperglycemia and may lead to loss of glycemic cont ol. These drugs include he hiazides and o her diuretics, corticoste oids, phenothiazines, hy oid p oducts, est ogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When hese drugs are administered to a patient receiving oral blood glucose-lowering agents, he patient should be observed for loss of glycemic cont ol. When these drugs are wi hdrawn from a patient receiving oral blood glucose-lowering agents, he patient should be observed closely for hypoglycemia.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term carcinogenicity studies were performed for 104 weeks at doses up to and including 120 mg/kg body weight/day (rats) and 500 mg/kg body weight/day (mice) or app oximately 60 and 125 times clinical exposure, respectively, on a mg/m^2 basis. No evidence of carcinogenicity was found in mice or female rats. In male rats, here was an increased incidence of benign adenomas of the hy oid and liver. The relevance of these findings to humans is unclear. The no-effect doses for hese observations in male rats were 30 mg/kg body weight/day for hy oid tumors and 60 mg/kg body weight/day for liver tumors, which are over 15 and 30 times, respectively, clinical exposure on a mg/m^2 basis.

Repaglinide was non-genotoxic in a battery of *in vivo* and *in vitro* studies: Bacterial mutagenesis (Ames test), *in vitro* forward cell mutation assay in V79 cells (HGPRT), *in vitro* ch omosomal aberration assay in human lymphocytes, unscheduled and replicating DNA synthesis in rat liver, and *in vivo* mouse and rat mic onucleus tests.

Fertility of male and female rats was unaffected by repaglinide administration at doses up to 80 mg/kg body weight/day (females) and 300 mg/kg body weight/day (males); over 40 times clinical exposure on a mg/m^2 basis.

Pregnancy

Pregnancy category C

Teratogenic Effects: Safety in pregnant women has not been established. Repaglinide was not teratogenic in rats or rabbits at doses 40 times (rats) and app oximately 0.8 times (rabbit) clinical exposure (on a mg/m^2 basis) h oughout pregnancy. Because animal rep oduction studies are not always predictive of human response, Repaglinide should be used during pregnancy only if it is clearly needed.

Because recent information suggests hat abnormal blood glucose levels during pregnancy are associated wi h a higher incidence of congenital abnormalities, many experts recommend hat insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Offspring of rat dams exposed to repaglinide at 15 times clinical exposure on a mg/m^2 basis during days 17 to 22 of gestation and during lactation developed nonteratogenic skeletal deformities consisting of shortening, hickening, and bending of he humerus during the postnatal period. This effect was not seen at doses up to 2.5 times clinical exposure (on a mg/m^2 basis) on days 1 to 22 of pregnancy or at higher doses given during days 1 to 16 of pregnancy. Relevant human exposure has not occurred to date and herefore he safety of Repaglinide administration h oughout pregnancy or lactation cannot be established.

Nursing Mothers

In rat rep oduction studies, measurable levels of repaglinide were detected in the breast milk of he dams and lowered blood glucose levels were observed in he pups. C oss fostering studies indicated that skeletal changes (see **Nonteratogenic Effects**) could be induced in cont ol pups nursed by treated dams, al hough his occurred to a lesser degree han those pups treated *in utero*. Al hough it is not known whe her repaglinide is excreted in human milk some oral agents are known to be excreted by this oute. Because he potential for hypoglycemia in nursing infants may exist, and because of he effects on nursing animals, a decision should be made as to whether Repaglinide should be discontinued in nursing mo hers, or if mo hers should discontinue nursing. If Repaglinide is discontinued and if diet alone is inadequate for cont olling blood glucose, insulin herapy should be considered.

Pediatric Use

No studies have been performed in pediatric patients.

Geriatric Use

In repaglinide clinical studies of 24 weeks or greater duration, 415 patients were over 65 years of age. In one-year, active-cont olled trials, no differences were seen in effectiveness or adverse events between hese subjects and hose less han 65 o her han he expected age-related increase in cardiovascular events observed for Repaglinide and comparator drugs. There was no increase in frequency or severity of hypoglycemia in older subjects. O her reported clinical experience has not identified differences in responses between he elderly and younger patients, but greater sensitivity of some older individuals to Repaglinide therapy cannot be ruled out.

ADVERSE REACTIONS

Hypoglycemia: See **PRECAUTIONS** and **OVERDOSAGE** sections.

Repaglinide has been administered to 2931 individuals during clinical trials. App oximately 1500 of hese individuals wi h type 2 diabetes have been treated for at least 3 mon hs, 1000 for at least 6 months, and 800 for at least 1 year. The majority of these individuals (1228) received Repaglinide in one of five 1-year, active-cont olled trials. The comparator drugs in these 1-year trials were oral sulfonylurea drugs (SU) including glyburide and glipizide. Over one year, 13% of Repaglinide patients were discontinued due to adverse events, as were 14% of SU patients. The most common adverse events leading to wi hdrawal were hyperglycemia, hypoglycemia, and related symptoms (see **PRECAUTIONS**). Mild or moderate hypoglycemia occurred in 16% of Repaglinide patients, 20% of glyburide patients, and 19% of glipizide patients.

The table below lists common adverse events for Repaglinide patients compared to bo h placebo (in trials 12 to 24 weeks duration) and to glyburide and glipizide in one year trials. The adverse event p ofile of Repaglinide was generally comparable to that for sulfonylurea drugs (SU).

Commonly Reported Adverse Events (% of Patients)*

EVENT	REPAGLINIDE N=352	PLACEBO N=108	REPAGLINIDE N=1228	SU N=498
	Placebo cont olled studies		Active cont olled studies	
Metabolic				
Hypoglycemia	31**	7	16	20
Respiratory				
URI	16	8	10	10
Sinusitis	6	2	3	4
Rhinitis	3	3	7	8
B onchitis	2	1	6	7
Gastrointestinal				
Nausea	5	5	3	2
Diar hea	5	2	4	6
Constipation	3	2	2	3
Vomiting	3	3	2	1
Dyspepsia	2	2	4	2
Musculoskeletal				
Ar hralgia	6	3	3	4
Back Pain	5	4	6	7
Other				
Headache	11	10	9	8
Pares hesia	3	3	2	1
Chest Pain	3	1	2	1
Urinary tract infection	2	1	3	3
Too h disorder	2	0	<1	<1
Allergy	2	0	1	<1

*: Events ≥ 2% for the Repaglinide g oup in he placebo cont olled studies and ≥ events in he placebo g oup
: See trial description in **CLINICAL PHARMACOLOGY, Clinical Trials

Cardiovascular Events

In one-year trials comparing Repaglinide to sulfonylurea drugs, the incidence of angina was comparable (1.8%) for both treatments, with an incidence of chest pain of 1.8% for Repaglinide and 1.0% for sulfonylureas. The incidence of o her selected cardiovascular events (hypertension, abnormal EKG, myocardial infarction, ar hythmias, and palpitations) was ≤ 1% and not different between Repaglinide and the comparator drugs.

The incidence of total serious cardiovascular adverse events, including ischemia, was higher for repaglinide (4%) than for sulfonylurea drugs (3%) in cont olled comparator clinical trials. In 1-year cont olled trials, Repaglinide treatment was not associated with excess mortality when compared to he rates observed wi h o her ora hypoglycemic agent herapies.

Summary of Serious Cardiovascular Events (% of total patients with events) in Trials Comparing Repaglinide to Sulfonylureas

	REPAGLINIDE	SU*
Total Exposed	1228	498
Serious CV Events	4%	3%
Cardiac Ischemic Events	2%	2%
Dea hs due to CV Events	0.5%	0.4%

*: glyburide and glipizide

Seven controlled clinical trials included Repaglinide combination herapy w th NPH-insulin (n=431), insulin formulations alone (n=388) or other combinations (sulfonylurea plus NPH-insulin) (n=120). There were six serious adverse events of myocardial ischemia in patients treated wi h Repaglinide plus NPH-insulin f om two studies, and one event in patients using insulin formulations alone f om another study.

Infrequent Adverse Events

(<1% of Patients)

Less common adverse clinical or laboratory events observed in clinical trials included elevated liver enzymes, h ombocytopenia, leukopenia, and anaphylactoid reactions.

Al hough no causal relationship with repaglinide has been established, postmarketing experience includes reports of he following rare adverse events: alopecia, hemolytic anemia, pancreatitis, Stevens-Johnson Synd ome, and severe hepatic dysfunction including jaundice and hepatitis.

Combination Therapy with Thiazolidinediones

During 24-week treatment clinical trials of Repaglinide- osiglitazone or Repaglinide-pioglitazone combination herapy (a total of 250 patients in combination herapy), hypoglycemia (blood glucose < 50 mg/dL) occurred in 7% of combination therapy patients in comparison to 7% for Repaglinide monotherapy, and 2% for hiazolidinedione mono herapy.

Peripheral edema was reported in 12 out of 250 Repaglinide-thiazolidinedione combination herapy patients and 3 out of 124 hiazolidinedione monotherapy patients, with no cases reported in these trials for Repaglinide monotherapy. When corrected for d opout rates of the treatment g oups, he percentage of patients having events of peripheral edema per 24 weeks of treatment were 5% for Repaglinide-hiazolidinedione combination therapy, and 4% for hiazolidinedione mono herapy. There were reports in 2 of 250 patients (0.8%) treated with Repaglinide- hiazolidinedione herapy of episodes of edema with congestive heart failure. Bo h patients had a prior history of co onary artery disease and recovered after treatment wi h diuretic agents. No comparable cases in he mono herapy treatment g oups were reported.

Mean change in weight f om baseline was +4.9 kg for Repaglinide-thiazolidinedione therapy. There were no patients on Repaglinide- hiazolidinedione combination therapy who had elevations of liver transaminases (defined as 3 times the upper limit of normal levels).

OVERDOSAGE

In a clinical trial, patients received increasing doses of Repaglinide up to 80 mg a day for 14 days. There were few adverse effects other than hose associated wi h the intended effect of lowering blood glucose. Hypoglycemia did not occur when meals were given wi h hese high doses. Hypoglycemic symptoms without loss of consciousness or neu ologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patte ns. Close monitoring may continue until he physician is assured hat 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 hat repaglinide is dialyzable using hemodialysis.

Severe hypoglycemic reactions wi h coma, seizure, or o her neu ological 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 concentrated (50%) glucose solution. This should be followed by a continuous infusion of more dilute (10%) glucose solution at a rate hat will maintain the blood glucose at a level above 100 mg/dL.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for he management of type 2 diabetes wi h Repaglinide.

The patient's blood glucose should be monitored periodically to determine he minimum effective dose for he patient; to detect primary failure, i.e., inadequate lowering of blood glucose at he maximum recommended dose of medication; and to detect secondary failure, i.e., loss of an adequate blood glucose-lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels are of value in monitoring he patient's longer term response to herapy.

Short-term administration of Repaglinide may be sufficient during periods of transient loss of cont ol in patients usually well cont olled on diet.

Repaglinide doses are usually taken wi hin 15 minutes of he meal but time may vary f om immediately preceding he meal to as long as 30 minutes before he meal.

Starting Dose

For patients not previously treated or whose HbA_{1c} is < 8%, he starting dose should be 0.5 mg with each meal. For patients previously treated with blood glucose-lowering drugs and whose HbA_{1c} is ≥ 8%, he initial dose is 1 or 2 mg w th each meal preprandially (see previous paragraph).

Dose Adjustment

Dosing adjustments should be determined by blood glucose response, usually fasting blood glucose. Postprandial glucose levels testing may be clinically helpful in patients whose pre-meal blood glucose levels are satisfactory but whose overall glycemic cont ol (HbA_{1c}) is inadequate. The preprandial dose should be doubled up to 4 mg with each meal until satisfactory blood glucose response is achieved. At least one week should elapse to assess response after each dose adjustment.

The recommended dose range is 0.5 mg to 4 mg taken wi h meals. Repaglinide may be dosed preprandially 2, 3, or 4 times a day in response to changes in he patient's meal patte n. The maximum recommended daily dose is 16 mg.

Patient Management

Long-term efficacy should be monitored by measurement of HbA_{1c} levels app oximately every 3 months. Failure to follow an app opriate dosage regimen may precipitate hypoglycemia or hyperglycemia. Patients who do not adhere to heir prescribed dietary and drug regimen are more p one to exhibit unsatisfactory response to herapy including hypoglycemia. When hypoglycemia occurs in patients taking a combination of Repaglinide and a thiazolidinedione the dose of Repaglinide should be reduced.

Patients Receiving Other Oral Hypoglycemic Agents

When Repaglinide is used to replace therapy wi h o her oral hypoglycemic agents, Repaglinide 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 f om longer half-life sulfonylurea agents (e.g., chlorp opamide) to repaglinide, close monitoring may be indicated for up to one week or longer.

Combination Therapy

If Repaglinide monotherapy does not result in adequate glycemic cont ol, a hiazolidinedione may be added. If hiazolidinedione monotherapy does not p ovide adequate cont ol, Repaglinide may be added. The starting dose and dose adjustments for Repaglinide combination therapy is he same as for Repaglinide monotherapy. The dose of each drug should be carefully adjusted to determine he minimal dose required to achieve he desired pharmacologic effect. Failure to do so could result in an increase in he incidence of hypoglycemic episodes. App opriate monitoring of FPG and HbA_{1c} measurements should be used to ensure that he patient is not subjected to excessive drug exposure or increased p obability of secondary drug failure.

HOW SUPPLIED

Repaglinide tablets, USP, 1 mg are available in he following form: Yellow, ound, biconvex tablets, debossed wi h "745" on one side and 'C' on he o her side.

Bottles of 100 NDC 57664-745-88
Bottles of 500 NDC 57664-745-13
Bottles of 1000 NDC 57664-745-18

Repaglinide tablets, USP, 2 mg are available in the following form: Pink, ound, biconvex tablets, debossed wi h "747" on one side and 'C' on he o her side.

Bottles of 100 NDC 57664-747-88
Bottles of 500 NDC 57664-747-13
Bottles of 1000 NDC 57664-747-18

Store at 20° to 25°C (68° to 77°F) [see USP Cont olled Room Temperature].
P otect f om moisture.
Keep bottles tightly closed.
Dispense in tight containers wi h safety closures.

Distributed by: Caraco Pharmaceutical Laboratories, Ltd. Iss.: 08/12
Det oit, MI 48202

Manufactured by: Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512

C.S. NO: 5465772

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/s/

LISA H KWOK
12/06/2012

CHI-ANN Y WU
12/06/2012
For Wm. Peter Rickman