For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

8024836-805

EUREPA MF

(Repaglinide And Metformin Hydrochloride Tablets)

COMPOSITION

EUREPA MF 1

Each film coated tablet contains :

Repaglinide U.S.P. 1 mg

Metformin Hydrochloride I.P. 500 mg

Colours : Yellow Oxide of Iron & Titanium Dioxide

EUREPA MF 2

Each film coated tablet contains :

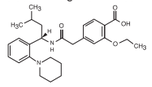
Repaglinide U.S.P. 2 mg

Metformin Hydrochloride I.P. 500 mg

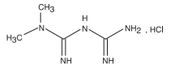
Colours : Red Oxide of Iron & Titanium Dioxide

DESCRIPTION

Repaglinide and Metformin Hydrochloride tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes. The concomitant use of Repaglinide and Metformin Hydrochloride has been previously approved based on clinical trials in patients with type 2 diabetes inadequately controlled on exercise, diet, and Metformin Hydrochloride alone. Repaglinide, (S)-2-Ethyoxy-4-[2-[[methyl-1-[2-[(1-piperidinyl)phenyl] butyl]amino]-2-oxoethyl]-benzoic acid is chemically unrelated to the oral sulfonylurea insulin secretagogues. Repaglinide is a White to off-white solid. Melts at about 132^{O}C to 136^{O}C. Soluble in methanol. Its molecular formula $C_{27}H_{36}N_2O_4$ and a molecular weight of 452.59 with the structural formula as shown below.



Metformin Hydrochloride is 1,1-dimethylbiguanide hydrochloride. It is white, crystalline powder, hygroscopic, with a molecular formula of $C_4H_{11}N_5$·HCl and a molecular weight of 165.6. The structural formula of Metformin Hydrochloride is :



Repaglinide and Metformin Hydrochloride is available as a tablet for oral administration containing 1 mg Repaglinide with 500 mg Metformin Hydrochloride (1 mg/500 mg) or 2mg Repaglinide with 500 mg Metformin Hydrochloride (2 mg/500 mg).

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Repaglinide and Metformin Hydrochloride tablet combines two anti-hyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes. Repaglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta (ß) cells in the pancreatic islets. Repaglinide closes ATP-dependent potassium channels in the ß-cell membrane by binding at characterizable sites. This potassium channel blockade depolarizes the ß-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.

Metformin is an anti-hyperglycemic agent, which improves glucose tolerance in patients with type 2 diabetes by lowering both the basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With Metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

PHARMACOKINETICS

The results of a bioequivalence study in healthy subjects demonstrated that (Repaglinide / Metformin Hydrochloride) 1 mg/500 mg and 2 mg/500 mg combination tablets are bioequivalent to coadministration of corresponding doses of Repaglinide and Metformin Hydrochloride as individual tablets. Repaglinide dose proportionality was demonstrated for Repaglinide and Metformin Hydrochloride tablet (2 mg/500 mg) and Repaglinide and Metformin Hydrochloride (1 mg/500 mg).

Mean (SD) Pharmacokinetic Parameters for Repaglinide and Metformin		
	Pharmacokinetic Parameter (N=55)	
Treatment	**AUC (ng·h/mL)**	**Cmax (ng/mL)**
Repaglinide		
A	34.5 (13.3)	26.0 (13.7)
B	35.0 (13.2)	23.7 (12.5)
C	17.6 (6.6)	12.9 (6.9)
Metformin		
A	6041.9 (1494.6)	838.8 (210.2)
B	5871.6 (1352.6)	805.9 (160.3)
C	5948.9 (1442.0)	799.4 (174.6)

A = 2 mg/500 mg Repaglinide + Metformin Hydrochloride Tablet
B = 2 mg Repaglinide tablet + 500 mg Metformin Hydrochloride Tablet
C = 1 mg/500 mg Repaglinide + Metformin Hydrochloride Tablet

Absorption and Bioavailability

Repaglinide: After single and multiple oral doses in healthy subjects or in patients with type 2 diabetes, peak plasma drug levels (Cmax) occur within 1 hour (Tmax). Repaglinide is 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 Tmax was not changed, but the mean Cmax and AUC (area under the time/plasma concentration curve) were decreased 20% and 12.4%, respectively.

Metformin Hydrochloride: The absolute bioavailability of a 500 mg Metformin Hydrochloride tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of Metformin Hydrochloride tablets of 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower peak concentration (Cmax), a 25% lower area under plasma concentration (AUC) and a 35-minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of Metformin Hydrochloride with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

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

Metformin Hydrochloride : The apparent volume of distribution (V/F) of Metformin following single oral dose of 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of Metformin Hydrochloride, steady state plasma concentrations of Metformin are reached within 24-48 hours and are generally < 1 µg/mL. During controlled clinical trials, maximum Metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Metabolism and Elimination

Repaglinide: Repaglinide is completely metabolized by oxidative biotransformation and direct conjugation with glucuronic acid after either an intravenous or oral dose. The major metabolites are an oxidized dicarboxylic acid (M2), the aromatic amine (M1), and the acyl glucuronide (M7). The cytochrome P-450 enzyme system, specifically 2C8 and 3A4, have been shown to be involved in the N-dealkylation of Repaglinide to M2 and the further oxidation to M1. Metabolites do not contribute to the glucose-lowering effect of Repaglinide. 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 approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound. The major metabolite (M2) accounted for 60% of the administered dose. Less than 2% of parent drug was recovered in feces.

Metformin Hydrochloride: Intravenous single-dose studies in normal subjects demonstrate that Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of Metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific populations

Renal Impairment

Because Repaglinide + Metformin contains Metformin Hydrochloride, it should not be used in patients with renal impairment

Repaglinide

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). Both AUC and Cmax of Repaglinide were similar in patients with 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 with severely reduced renal function had elevated mean AUC and Cmax 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.

Metformin Hydrochloride

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of Metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Impairment

Repaglinide and Metformin Hydrochloride should be avoided in patients with hepatic impairment

Repaglinide

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 healthy: 91.6 ng/mL*hr; AUC CLD patients: 368.9 ng/mL*hr; Cmax, healthy: 46.7 ng/mL; Cmax, CLD 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 usual doses. Therefore, Repaglinide should generally be avoided in patients with impaired liver function.

Metformin Hydrochloride

No pharmacokinetics studies with Metformin Hydrochloride have been conducted in patients with hepatic impairment.

Geriatric Patients

Healthy volunteers treated with Repaglinide 2 mg before each of 3 meals, showed no significant differences in Repaglinide pharmacokinetics between the group of patients <65 years of age and those ≥ 65 years of age. Limited data from controlled pharmacokinetic studies of Metformin Hydrochloride in healthy elderly subjects suggest that total plasma clearance is decreased, the half-life is prolonged, and Cmax is increased, compared to healthy young subjects. From these data, it appears that the change in Metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

INDICATIONS AND USAGE

Repaglidine and Metformin Hydrochloride tablet is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a Meglitinide and Metformin Hydrochloride or who have inadequate glycemic control on a Meglitinide alone or Metformin Hydrochloride alone.

Important Limitations of Use:

Repaglinide and Metformin Hydrochloride tablet should not be used in patients with type-1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

CONTRAINDICATIONS

FDC of Repaglinide and Metformin Hydrochloride is contraindicated in:

- Renal impairment (e.g., serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females], or abnormal creatinine clearance).
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- Patients receiving both gemfibrozil and itraconazole.
- Patients with known hypersensitivity to Repaglinide, Metformin Hydrochloride or any inactive ingredients in Repaglinide and Metformin Hydrochloride.

WARNINGS AND PRECAUTIONS

Lactic Acidosis

Metformin hydrochloride

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to Metformin accumulation during treatment with Repaglinide and Metformin Hydrochloride; When it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When Metformin is implicated as the cause of lactic acidosis, Metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving Metformin Hydrochloride is very low (Approximately 0.03 cases/1,000 patient-years of exposure, with approximately 0.015 fatal cases/1,000 patient-years of exposure).

Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal impairment and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking Repaglinide and Metformin Hydrochloride and by use of the minimum effective dose of Repaglinide and Metformin Hydrochloride tablet. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Treatment with FDC of Repaglinide and Metformin Hydrochloride should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, Repaglinide and Metformin Hydrochloride should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, Repaglinide and Metformin Hydrochloride tablet should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking Repaglinide and Metformin Hydrochloride tablet, since alcohol potentiates the effects of Metformin on lactate metabolism. In addition, Repaglinide and Metformin Hydrochloride tablet should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure. The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Assessment of Renal Function

Metformin is substantially excreted by the kidney and the risk of Metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, patients with renal impairment should not receive Repaglinide and Metformin Hydrochloride tablet. Before initiation of therapy with Repaglinide and Metformin Hydrochloride tablet and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal impairment is anticipated, renal function should be assessed more frequently and Repaglinide and Metformin Hydrochloride tablet discontinued if evidence of renal impairment is present.

Radiologic Studies with Intravascular Iodinated Contrast Materials

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving Metformin Hydrochloride.

Therefore, in patients in whom any such study is planned, Repaglinide and Metformin Hydrochloride tablet should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Impaired Hepatic Function

Hepatic impairment has been associated with some cases of lactic acidosis. Therefore, Repaglinide and Metformin Hydrochloride tablet should generally be avoided in patients with hepatic impairment.

Alcohol Intake

Alcohol potentiates the effect of Metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving Repaglinide and Metformin Hydrochloride tablet.

Combination with NPH-insulin

Repaglinide

Repaglinide is not indicated for use in combination with NPH-insulin.

Drug Interactions

Gemfibrozil increases exposures to Repaglinide, one of the components of Repaglinide and Metformin Hydrochloride tablet, which may enhance and prolong the blood glucose lowering effects of Repaglinide.

Hypoglycemia

Most blood glucose-lowering drugs, including Repaglinide, can cause hypoglycemia. Patients who have not previously been treated with a Meglitinide should be started on the lowest available Repaglinide component of Repaglinide and Metformin Hydrochloride tablet to reduce the risk of hypoglycemia. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemia. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking β-adrenergic blocking drugs.

Vitamin B_{12} Levels

Measurement of hematologic parameters on an annual basis is advised in patients on Repaglinide and Metformin Hydrochloride tablet and any apparent abnormalities should be appropriately investigated and managed.

Surgical Procedures

Use of Repaglinide and Metformin Hydrochloride tablet should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

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 temporary loss of glycemic control may occur. At such times, it may be necessary to withhold Repaglinide and Metformin Hydrochloride tablet and temporarily administer insulin. Repaglinide and Metformin Hydrochloride tablet may be reinstituted after the acute episode is resolved.

Use of Concomitant Medications Affecting Renal Function or Metformin Disposition

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion should be used with caution.

Hypoxic States

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients receiving Repaglinide and Metformin Hydrochloride tablet, the drug should be promptly discontinued.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes

A patient with type 2 diabetes previously well-controlled on Repaglinide and Metformin Hydrochloride tablet who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. If acidosis of either form occurs, Repaglinide and Metformin Hydrochloride tablet must be stopped immediately and other appropriate corrective measures initiated.

Pregnancy

Pregnancy Category C.

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy.

Careful monitoring of glucose control is essential in these patients. Animal reproduction studies have not been conducted with repaglinide and metformin hydrochloride. It is not known whether repaglinide and metformin hydrochloride or its individual components can cause fetal harm when administered to a pregnant woman. Repaglinide and metformin hydrochloride should be given to a pregnant woman only if clearly needed.

Repaglinide

Repaglinide was not teratogenic in rats at doses 40 times, and rabbits approximately 0.8 times the clinical exposure (on a mg/m2 basis) throughout pregnancy. Offspring of rat dams exposed to repaglinide at 15 times clinical exposure on a mg/m2 basis during days 17 to 22 of gestation and during lactation developed nonteratogenic 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 clinical exposure (on a mg/m2 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 therefore the safety of repaglinide administration throughout pregnancy or lactation cannot be established.

Metformin Hydrochloride

Metformin HCl alone was not teratogenic in rats or rabbits at doses up to 600 mg/kg/day. This represents an exposure of approximately two and six times the near-maximal efficacious human daily dose of 2000 mg of the metformin hydrochloride component of Repaglinide and metformin hydrochloride based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers

No studies in lactating animals have been conducted with the Repaglinide and metformin hydrochloride fixed dose combination. In studies performed with individual components, both repaglinide and metformin are excreted into milk of lactating rats.

Repaglinide

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. Cross fostering studies indicated that skeletal changes could be induced in control pups nursed by treated dams, although this occurred to a lesser degree than those pups treated in utero.

Metformin hydrochloride

Studies in lactating rats with metformin hydrochloride show that it is excreted into milk and reaches levels comparable to those in plasma. It is not known whether repaglinide or metformin are excreted in human milk. Repaglinide and metformin hydrochloride is not recommended in nursing mothers because it may potentially cause hypoglycemia in nursing infants.

Pediatric Use

Safety and effectiveness of Repaglinide and metformin hydrochloride in pediatric patients have not been established. Repaglinide and metformin hydrochloride is not recommended for use in children.

Geriatric Use

Healthy volunteers treated with repaglinide 2 mg before each of 3 meals, showed no significant differences in repaglinide pharmacokinetics between the group of patients <65 years of age and those ≥65 years of age.

In patients with advanced age, Repaglinide and metformin hydrochloride should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, dose adjustment of Repaglinide and metformin hydrochloride should be based on a careful assessment of renal function.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Repaglinide

In a 104-week carcinogenicity study in rats at doses up to 120 mg/kg/day, the incidences of benign adenomas of the thyroid and liver were increased in male rats. The higher incidences of thyroid and liver tumors in male rats were not seen at lower dose of 30 mg/kg/day and 60 mg/kg/day respectively (which are over 15 and 30 times, respectively, clinical exposures on a mg/m^2 basis). In a 104-week carcinogenicity study in mice at doses up to 500 mg/kg/day, no evidence of carcinogenicity was found in mice (which is approximately 125 times 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 chromosomal aberration assay in human lymphocytes, unscheduled and replicating DNA synthesis in rat liver, and in vivo mouse and rat micronucleus tests. In a rat fertility study, Repaglinide was administered to male and female rats at doses up to 300 and 80 mg/kg/day, respectively. No adverse effects on fertility were observed (which are over 40 times clinical exposure on a mg/m^2 basis).

Metformin Hydrochloride

In a 104-week carcinogenicity study in rats at doses up to 900 mg/kg/day, the incidences of benign stromal uterine polyps were increased in female rats at 900 mg/kg/day (which is approximately four times the maximal recommended human daily dose of 2000 mg of Metformin Hydrochloride component of Repaglinide and Metformin Hydrochloride tablet on a mg/m^2 basis). In a 91-week carcinogenicity study in mice at doses up to 1500 mg/kg/day, no evidence of carcinogenicity was found in mice (which is approximately four times the maximal recommended human daily dose of 2000 mg of Metformin Hydrochloride component of Repaglinide and Metformin Hydrochloride tablet on a mg/m^2 basis).

There was no evidence of a mutagenic potential of Metformin Hydrochloride alone in the following in vitro tests: Ames test (S. typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative. In a rat fertility study, Metformin Hydrochloride was administered to male and female rats at doses up to 600 mg/kg/day. No adverse effects on fertility were observed (which is approximately three times the maximal recommended human daily dose of 2000 mg of Metformin Hydrochloride component of Repaglinide and Metformin Hydrochloride tablet on a mg/m^2 basis.)

ADVERSE REACTIONS

Most Frequently Observed Adverse Reactions

Repaglinide

In clinical trials of Repaglinide, hypoglycemia is the most common adverse reaction (> 5%) leading to withdrawal of patients treated with Repaglinide.

Metformin Hydrochloride

Gastrointestinal reactions (e.g., diarrhea, nausea, vomiting) are the most common adverse reactions (> 5%) with Metformin Hydrochloride treatment and are more frequent at higher Metformin Hydrochloride doses.

Patients with Inadequate Glycemic Control on Metformin Hydrochloride Monotherapy

Table 1 Summarizes the most common adverse reactions occurring in a 6-month randomized study of Repaglinide added to Metformin Hydrochloride in patients with type-2 diabetes inadequately controlled on Metformin Hydrochloride alone. Adverse reaction reported (regardless of Investigator Assessment of Causality) in ≥ 10 % of patients receiving combination therapy *

	Coadministered Repaglinide and Metformin Hydrochloride (N %)	Metformin Hydrochloride monotherapy (N %)	Repaglinide monotherapy (N %)
No. of Patients Exposed	27	27	28
Gastrointestinal			
System Disorder	9(33)	13(48)	10(36)
Diarrhea	5(19)	8(30)	2(7)
Nausea	4(15)	2(7)	1(4)
Symptomatic			
Hypoglycemia **	9(33)	0(0)	3(11)
Headache	6(22)	4(15)	3(11)
Upper Respiratory Tract Infection	3(11)	3(11)	3(11)

* Intent to treat population

** There were no cases of severe hypoglycemia (Hypoglycemia requiring the assistance of anther person)

Cardiovascular Events in Repaglinide monotherapy trials

In one-year trials comparing Repaglinide to sulfonylurea drugs, the incidence of angina was 1.8% for both treatments, with an incidence of chest pain of 1.8% for Repaglinide and 1.0% for sulfonylureas. The incidence of other selected cardiovascular events (hypertension, abnormal electrocardiogram, myocardial infarction, arrhythmias, 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 (51/1228 or 4%) than for sulfonylurea drugs (13/498 or 3%). In 1- year controlled trials, Repaglinide treatment was not associated with excess mortality when compared to the rates observed with other oral hypoglycemic agent therapies such as glyburide and glipizide. There were six serious adverse events of myocardial ischemia in patients treated with Repaglinide plus NPH-insulin (1.4%) from two studies, and one event in patients using insulin formulations alone from another study (0.3%).

Postmarketing experience with repaglinide includes infrequent reports of the following adverse events; alopecia, hemolytic anemia, pancreatitis, Stevens-Johnson Syndrome, and severe hepatic dysfunction including jaundice and hepatitis.

DRUG INTERACTIONS

Cationic Drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with Metformin by competing for common renal tubular transport systems. Careful patient monitoring and dose adjustment of Repaglinide and Metformin Hydrochloride tablet and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

CYP2C8 and CYP3A4 Inhibitors/Inducer

Repaglinide is metabolized by CYP2C8 and to a lesser extent by CYP3A4. Drugs that inhibit 2C8 (gemfibrozil, trimethoprim), inhibit 3A4 (itraconazole, ketaconazole), or induce CYP2C8/3A4 (rifampin) may alter the pharmacokinetics and pharmacodynamics of Repaglinide. In vivo data from a study that evaluated the co-administration of gemfibrozil and Repaglinide in healthy subjects showed a significant increase in Repaglinide blood levels. Administration of Repaglinide and Metformin Hydrochloride tablet and gemfibrozil to the same patient is not recommended.

DOSAGE AND ADMINISTRATION

Recommended Dosing

The dosage of Repaglinide and Metformin Hydrochloride tablet should be individualized on the basis of the patient's current regimen, effectiveness and tolerability. Repaglinide and Metformin Hydrochloride tablet can be administered 2 to 3 times a day up to a maximum daily dose of 10 mg Repaglinide/2500 mg Metformin Hydrochloride. No more than 4 mg Repaglinide/1000 mg Metformin Hydrochloride should be taken per meal. Initiation and maintenance of combination therapy with Repaglinide and Metformin Hydrochloride tablet should be individualized to the patient, and at the discretion of the health care provider. Blood glucose monitoring should be performed to determine the therapeutic response to Repaglinide and Metformin Hydrochloride tablet. Repaglinide and Metformin Hydrochloride tablet doses should usually be taken within 15 minutes prior to the meal but the timing can vary from immediately preceding the meal up to 30 minutes before the meal. Patients who skip a meal should be instructed to skip the Repaglinide and Metformin Hydrochloride tablet dose for that meal.

Patients Inadequately Controlled with Metformin Hydrochloride Monotherapy

If therapy with a combination tablet containing Repaglinide and Metformin Hydrochloride is considered appropriate for a patient with type 2 diabetes mellitus inadequately controlled with Metformin Hydrochloride alone, the recommended starting dose of Repaglinide and Metformin Hydrochloride tablet is 1mg Repaglinide / 500mg Metformin Hydrochloride administered twice daily with meals, with gradual dose escalation (based on glycemic response) to reduce the risk of hypoglycemia with Repaglinide.

Patients Inadequately Controlled with Meglitinide Monotherapy

If therapy with a combination tablet containing repaglinide and metformin Hydrochloride is considered appropriate for a patient with type 2 diabetes mellitus inadequately controlled with repaglinide alone, the recommended starting dose of the metformin Hydrochloride component of Repaglinide and Metcormin Hydrochloride tablet should be 500 mg metformin Hydrochloride twice a day, with gradual dose escalation (based on glycemic response) to reduce gastrointestinal side effects associated with metformin Hydrochloride.

Patients Currently Using Repaglinide and Metformin Hydrochloride Concomitantly

For patients switching from repaglinide co-administered with metformin Hydrochloride, Repaglinide and Metcormin Hydrochloride tablet can be initiated at the dose of repaglinide and metformin Hydrochloride similar to (but not exceeding) the patient's current doses, then may be titrated to the maximum daily dose as necessary to achieve targeted glycemic control.

OVERDOSAGE

Repaglinide

In a clinical trial, dizziness, headache, and diarrhea were reported in subjects receiving increasing doses of Repaglinide up to 80 mg a day for 14 days. 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. 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. 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 concentrated (50%) glucose solution. This should be followed by a continuous infusion of more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL.

Metformin Hydrochloride

Overdose of Metformin Hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with Metformin Hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of Metformin Hydrochloride overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom Metformin Hydrochloride overdosage is suspected.

EXPIRY DATE

Do not use later than the date of expiry

STORAGE

Store at a temperature not exceeding 30^{O}C, protected from moisture.

Keep out of reach of children

PRESENTATION

EUREPA MF 1 & EUREPA MF 2 are available in strip of 10 tablets.

torrent

Manufactured by :

TORRENT PHARMACEUTICALS LTD.

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Teh. Nalagarh, Dist. Solan (H.P.), INDIA.