CENTER FOR DRUG EVALUATION AND RESEARCH

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Prelay™
(Troglitazone) Tablets

WARNINGS

Hepatotoxicity

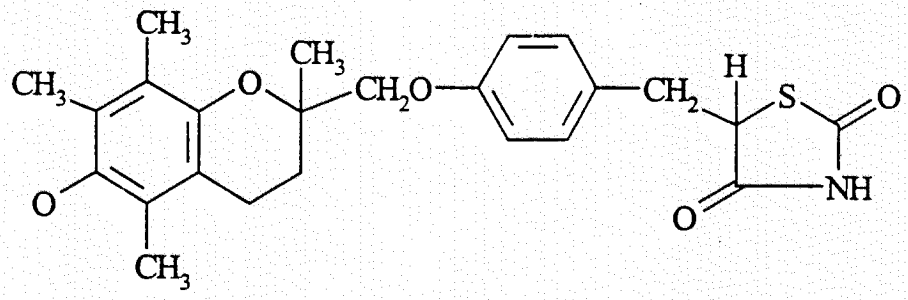
Severe idiosyncratic hepatocellular injury has been reported during marketed use (see ADVERSE REACTIONS). The hepatic injury is usually reversible, but very rare cases of hepatic failure, leading to death or liver transplant, have been reported.

During all clinical studies in North America, a total of 48 of 2510 (1.9%) Prelay-treated patients and 3 of 475 (0.6%) placebo-treated patients had ALT levels greater than 3 times the upper limit of normal. Nineteen patients (0.8%) had ALT over 8x ULN, 5 patients (0.2%) had ALT values over 30x ULN. Twenty of the Prelay-treated and one of the placebo-treated patients were withdrawn from treatment. Two of the 20 Prelay-treated patients developed reversible jaundice; one of these patients had a liver biopsy which was consistent with an idiosyncratic drug reaction. An additional Prelay-treated patient had a liver biopsy which was also consistent with an idiosyncratic drug reaction. (See ADVERSE REACTIONS, Laboratory Abnormalities.)

Serum alanine transaminase levels should be checked at the start of therapy, at least monthly for the first year of Prelay therapy, and at least quarterly thereafter. Prelay therapy should not be initiated if the patient has a history of liver disease, clinical evidence of active liver disease, alcohol abuse, or increased serum alanine transaminase levels (ALT >1.5 times the upper limit of normal). (See CONTRAINDICATIONS.) Liver function tests should also be obtained for patients at the first symptoms suggestive of hepatic dysfunction, fatigue, anorexia, nausea, vomiting, abdominal pain, dark urine or jaundice. If serum transaminase levels are moderately increased (ALT >1.5 to 2 times the upper limit of normal), liver function tests should be repeated immediately and then weekly until the levels return to normal. If at the time a patient has jaundice or ALT rises above 3 times the upper limit of normal, Prelay should be discontinued.

DESCRIPTION

Prelay™ (troglitazone) is an oral antihyperglycemic agent which acts primarily by decreasing insulin resistance. Prelay is used in the management of type 2 diabetes (noninsulin-dependent diabetes mellitus (NIDDM) also known as adult-onset diabetes). It improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Troglitazone (±-5-[[4-[3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione) is not chemically or functionally related to either the sulfonylureas, the biguanides, or the α-glucosidase inhibitors. The molecule contains 2 chiral centers, with each of the 4 stereoisomers having similar pharmacologic effects. The structural formula is as shown:



Troglitazone is a white to yellowish crystalline compound; it may have a faint, characteristic odor. Troglitazone has a molecular formula of $C_{24}H_{27}NO_5S$ and a molecular weight of 441.55 daltons. It is soluble in N,N-dimethylformamide or acetone; sparingly soluble in ethyl acetate; slightly soluble in acetonitrile, anhydrous ethanol, or ether; and practically insoluble in water.

Prelay is available as 200-, 300- and 400-mg tablets for oral administration formulated with the following excipients: croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polysorbate 80, povidone, purified water, silicon dioxide, titanium dioxide, and synthetic iron oxides.

CLINICAL PHARMACOLOGY

Mechanism of Action

Troglitazone is a thiazolidinedione antidiabetic agent that lowers blood glucose by improving target cell response to insulin. It has a unique mechanism of action that is dependent on the presence of insulin for activity. Troglitazone decreases hepatic glucose output and increases insulin-dependent glucose disposal in skeletal muscle. Its mechanism of action is thought to involve binding to nuclear receptors Peroxisome Proliferator Activated Receptor (PPAR) that regulate the transcription of a number of insulin responsive genes critical for the control of glucose and lipid metabolism. Unlike sulfonylureas, troglitazone is not an insulin secretagogue.

In animal models of diabetes, troglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. Plasma lactate and ketone body formation are also decreased. The metabolic changes produced by troglitazone result from the increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance. Treatment with troglitazone did not affect pancreatic weight, islet number or glucagon content, but did increase regranulation of the pancreatic beta cells in rodent models of insulin resistance.

Since troglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Maximum plasma concentration (Cmax) and the area under plasma concentration-time curve (AUC) of troglitazone increase proportionally with increasing doses over the dose range of 200 to 600 mg/day (Table 1). Following daily drug administration, steady-state plasma concentrations of troglitazone are reached within 3 to 5 days.

TABLE 1. Mean (±1 SD) Steady-State Pharmacokinetics of Troglitazone in 21 Normal Volunteers

Dose (mg/day)	Cmax (μg/mL)	AUC(0-24) (μg•hr/mL)	CL/F* (mL/min)
200	0.90 (0.36)	7.4 (2.4)	500 (187)
400	1.61 (0.69)	13.4 (5.5)	601 (324)
600	2.82 (1.03)	22.1 (6.8)	496 (166)

* CL/F = Apparent oral clearance.

Absorption: Troglitazone is absorbed rapidly following oral administration; the time for maximum plasma concentration (tmax) occurs within 2 to 3 hours. Food increases the extent of absorption by 30% to 85%; thus Prelay should be taken with a meal to enhance systemic drug availability.

Distribution: Mean apparent volume of distribution (V/F) of troglitazone following multiple-dose administration ranges from 10.5 to 26.5 L/kg of body weight. Troglitazone is extensively bound (>99%) to serum albumin. [^{14}C]troglitazone partitions into red blood cells (~5% of whole blood radioactivity).

Metabolism: In 6 healthy male volunteers given a single 400-mg dose of [^{14}C]troglitazone after 14 days of treatment with 400-mg troglitazone tablets, the major metabolites found in the plasma were the sulfate conjugate (Metabolite 1), followed by the quinone metabolite (Metabolite 3). Only 3.1% of the dose was detected in the urine; this was primarily in the form of the glucuronide conjugate (Metabolite 2), which is present in negligible amounts in the plasma. In both normal volunteers and patients with type 2 diabetes, steady-state levels of Metabolite 1 are 6 to 7 times that of troglitazone and Metabolite 3.

Troglitazone incubated with expressed human P450 1A1, 1A2, 2A6, 2B6, 2D6, 2E1, and 3A4 in the presence and absence of known inhibitors of these enzymes showed no Metabolite 3 formation above levels in control samples. Studies in human microsomes suggest that Metabolite 3 is not subject to further metabolism by the major P450 isozymes. Troglitazone did not inhibit any of the major P450 enzymes at clinically relevant concentrations. The inhibitory characteristics of Metabolite 3 have not been investigated directly.

The results of human *in vivo* drug interaction trials suggest that troglitazone induces cytochrome P450 3A4 at clinically relevant doses (see Drug Interactions).

Excretion: Following oral administration of [^{14}C]troglitazone, approximately 88% of the radioactivity is recovered in feces (85%) and urine (3%). Unchanged troglitazone is not recovered in urine following oral administration. Mean plasma elimination half-life of troglitazone ranges from 16 to 34 hours.

Special Populations

Renal Insufficiency: In patients with various degrees of renal function, the apparent clearance of total and unbound troglitazone and the plasma elimination half-life of troglitazone, Metabolite 1, and Metabolite 3 do not correlate with creatinine clearance. Thus, dose adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Troglitazone, Metabolite 1, and Metabolite 3 plasma concentrations in patients with chronic liver disease (Childs-Pugh Grade B or C) were increased by approximately 30%, 400% and 100%, respectively, compared to those in healthy subjects without hepatic dysfunction. There was no change in plasma protein binding. No adverse events were noted in any group that were attributed to drug. However, Prelay therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >1.5 times the upper limit of normal); see WARNINGS.

Geriatrics: Steady-state pharmacokinetics of troglitazone, Metabolite 1, and Metabolite 3 in healthy elderly subjects are comparable to those seen in young adults.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of troglitazone and its metabolites are similar in men and women.

Ethnicity: Pharmacokinetics of troglitazone and its metabolites are similar among various ethnic groups.

Pharmacodynamics and Clinical Effects

Clinical studies demonstrate that Prelay improves insulin sensitivity in insulin-resistant patients. Prelay increases insulin-dependent glucose disposal, reduces hepatic gluconeogenesis, and enhances cellular responsiveness to insulin and thus, improves dysfunctional glucose homeostasis. In patients with type 2 diabetes, the decreased insulin resistance produced by Prelay causes decreases in serum glucose, plasma insulin, and hemoglobin A_{1C}. Unlike sulfonylureas, Prelay does not stimulate insulin secretion. Addition of Prelay to a sulfonylurea has a synergistic effect since both agents act to improve glucose tolerance by different but complimentary mechanisms. These effects persist for 124 weeks of Prelay treatment.

In clinical trials of Prelay, an increase in LDL (up to 13%), HDL (up to 16%), and total cholesterol (total-C) (up to 5%) occurred while total-C/HDL and LDL/HDL ratios did not change. The increase in total cholesterol is due to the increase in HDL and LDL cholesterol. Despite the observed increase in total and LDL cholesterol, ApoB fraction levels are not increased. Treatment with troglitazone decreases plasminogen activator inhibitor type 1 (PAI-1) independent of glycemic control. The clinical significance of this is not known. Patients treated with Prelay exhibited a reduction in free fatty acids (up to 22%) and a reduction in fasting (-13% to –26%) and postprandial triglyceride levels. For patients on Prelay and insulin, reduction in insulin doses may occur following Prelay therapy and some attenuation of the triglyceride reduction may occur.

Pharmacokinetic estimators of systemic troglitazone exposure do not improve the prediction of pharmacodynamic response beyond that obtained based upon knowledge of the administered dose.

Prelay has only been shown to exert its antihyperglycemic effect in the presence of insulin. Because Prelay does not stimulate insulin secretion, hypoglycemia in patients treated with Prelay alone is not to be expected. Because of this insulin-dependent mechanism of action, Prelay should not be used in patients with type 1 diabetes.

Clinical Studies

Combination With Sulfonylureas

A 52-week, double-blind, placebo-controlled study of Prelay and 12 mg micronized glyburide, alone and in combination, was conducted in patients with type 2 diabetes (N = 552), who had failed to achieve adequate glycemic control (FSG of 224 mg/dL and HbA_{1C} of 9.6%) while on maximal doses of a sulfonylurea. Patient randomized to receive micronized glyburide showed mean increases in FSG and HbA_{1C}. Similarly, patients who switched from a sulfonylurea to Prelay monotherapy also demonstrated an increase in FSG and HbA_{1C}.

TABLE 2. Combination Therapy With Glyburide
Mean Difference From 12 mg Micronized
Glyburide Monotherapy (1yr)

	200 mg Prelay + Glyburide	400 mg Prelay + Glyburide	600 mg Prelay + Glyburide
FSG (mg/dL)			
Mean Baseline	226	231	220
Adjusted Mean Change from Baseline	-31	-38	-56
Adjusted Mean Difference from Glyburide	-54**	-61**	-79**
HbA_{1C} (%)			
Mean Baseline	9.5	9.7	9.5
Adjusted Mean Change from Baseline	-0.7	-0.9	-1.8
Adjusted Mean Difference from Glyburide	-1.6**	-1.8**	-2.7**
Insulin(μU/mL)			
Mean Baseline	28.2	24.9	26.4
Adjusted Mean Change from Baseline	-3.8	-5.9	-6.1
Adjusted Mean Difference from Glyburide	-2.4	-4.4*	-4.6*

* $p<0.05$ compared to continuation of glyburide monotherapy.
** $p< 0.0001$ compared to continuation of glyburide monotherapy.

TABLE 3. Combination Therapy With Glyburide:
Percent of Patients Achieving Glycemic
Control at End of Study (1yr)

Prelay (mg)	0	200	400	600
Glyburide (mg)	12	12	12	12
HbA_{1C} (%)				
≤ 7%	1	22	21	41
≤ 8%	10	33	33	60

A combination of 200, 400, and 600 mg of Prelay with micronized glyburide achieved lower levels of fasting plasma glucose and HbA_{1C} levels than either agent achieved alone (see Tables 2 and 3). These improvements in glycemic control were associated with mean weight gains of 5.8 to 13.1 pounds. To eliminate weight as a confounding factor in this study, patients had been instructed to follow a diet to maintain current weight.

Combination With Sulfonylurea and Metformin

In a 24-week, double-blind, randomized study in patients with type 2 diabetes (N = 196) who have failed to achieve glycemic control with the combination of a sulfonylurea and metformin either Prelay or placebo were added. Patients randomized to receive a sulfonylurea with metformin and 400 mg of troglitazone, showed mean decreases in FPG and HbA_{1c} (-43 mg/dL and -1.3%, respectively). Similarly, there was a 9% reduction in endogenous insulin, a 10% increase in fasting C-peptide, and a 9% increase in HDL. Forty-three percent of subjects receiving the combination of sulfonylurea, metformin, and troglitazone achieved adequate glycemic control of less than 8% HbA_{1c} ($p < 0.001$) while only 6% of patients achieved control with the sulfonylurea, metformin, and placebo combination (Table 4).

TABLE 4. Triple Therapy (Sulfonylurea and Metformin plus or minus Troglitazone) Change From Baseline Glycemic Parameters After 24 Weeks of Double-Blind Treatment

	Sulfonylurea[b]/Metformin (<2.0 g/d)		Sulfonylurea[b]/Metformin (≥2.0 g/d)	
	Placebo	Troglitazone	Placebo	Troglitazone
N	47	33	47	60
Baseline HbA_{1c} (%)	9.6	9.6	9.6	9.5
Adjusted Mean Change[a]	0.3	-1.7	0	-1.1
Adjusted Mean Difference from Placebo		-1.9		-1.1
Baseline, FSG (mg/dL)	231	220	228	234
Adjusted Mean Change	6	-57	3	-38
Adjusted Mean Difference		-63		-41

[a] Change means value at 24 weeks minus value at baseline

[b] All patients were on maximum tolerated doses of any sulfonylurea

Combination With Insulin

Two clinical studies were conducted to evaluate the effects of Prelay on glycemic control and insulin dose in patients with type 2 diabetes who were being treated with insulin.

In one 6-month, double-blind, placebo-controlled study in insulin-treated type 2 diabetic patients receiving a mean of 73 (range 27-143) units/day of insulin with a mean baseline HbA_{1C} of 9.42 (range 7.04-12.48), Prelay (200 or 600 mg/day) or placebo was added to the insulin therapy. Investigators were instructed to reduce insulin doses only if two consecutive FSGs were ≤100 mg/dL. Prelay-treated patients showed a significant ($p < 0.0001$) reduction in HbA_{1C} compared with patients who received placebo (see Table 5).

Thirty percent of patients treated with 200 mg Prelay and 57% of patients treated with 600 mg Prelay had an HbA_{1C} value below 8% at the end of the study compared with 11% of placebo-treated patients. Accompanying this improvement in glycemic control was a significant ($p < 0.0001$) decrease in exogenous insulin dosage of 15% in the 200-mg Prelay treatment group and 42% in the 600-mg Prelay treatment group compared with 1% in the placebo group. HbA_{1C} values and insulin dose as a function of duration of Prelay treatment are presented in Figures 1 and 2.

TABLE 5. Combination Therapy With Insulin—
Mean Change From Baseline at 6 Months

Parameter	Placebo	Troglitazone 200 mg	Troglitazone 600 mg
N	118	116	116
HbA_{1C} (%)			
Mean Baseline (SE)	9.43 (0.10)	9.51 (0.10)	9.32 (0.11)
Mean Change from Baseline (SE)[1]	-0.12 (0.10)	-0.84 (0.10)	-1.41 (0.10)
Adjusted Mean Difference from Placebo (SE)	–	-0.72 (0.14)*	-1.29 (0.14)*
Percent Mean Change from Baseline	-1.3	-8.8	-15.1
Insulin Daily Dosage, Units			
Mean Baseline (SE)	75 (3.3)	73 (3.4)	71 (2.9)
Mean Change from Baseline (SE)	1 (2.1)	-11 (2.1)	-29 (2.2)
Adjusted Mean Difference from Placebo (SE)	–	-12 (3.0)*	-30 (3.0)*
Percent Mean Change from Baseline	1	-15	-42

* $p \leq 0.0001$
[1]Least squares mean adjusted for investigator center and baseline

Figure 1. Combination Therapy With Insulin, Mean Change from Baseline for HbA_{1C}.

Figure 2. Combination Therapy With Insulin, Mean Change from Baseline for Insulin Dose.

A second 6-month, double-blind, placebo-controlled study in insulin-treated type 2 diabetics who previously were poorly controlled on oral agents receiving 30 to 150 units insulin/day assessed the use of Prelay in reducing exogenous insulin dosage while improving glycemic control as measured by capillary blood glucose.

Patients treated with 200-mg (N = 75) and 400-mg (N = 76) Prelay had their insulin doses decreased by 41% and 58%, respectively, compared to a reduction of insulin dose in the placebo group (N = 71) of 14% while maintaining or improving glycemic control. Forty-one percent of the patients in the 400-mg group decreased their insulin injection frequency an average from 3 to 1 injections per day; 19% of patients receiving placebo decreased their injection frequency an average from 3 to 2 injections per day. Insulin therapy was discontinued in 15% of patients in the 400-mg Prelay group compared to 7% in the 200-mg group and 1.5% in the placebo group.

A greater than 50% reduction in insulin dose was achieved by 51% of patients on 200 mg and 70% on 400 mg once daily as compared to 17% on placebo.

INDICATIONS AND USAGE

Prelay is indicated to improve glycemic control in patients with type 2 diabetes mellitus as an adjunct to diet and exercise in combination with (not substituted for):

- A sulfonylurea drug for patients who are not adequately controlled with a sulfonylurea alone, or
- A sulfonylurea drug together with metformin for patients who are not adequately controlled with the combination of a sulfonylurea and metformin, or
- Insulin in patients who are not adequately controlled with insulin alone.

Prelay is not indicated as initial therapy in patients with type 2 diabetes.

CONTRAINDICATIONS

Prelay is contraindicated in patients with known hypersensitivity or allergy to Prelay or any of its components. Prelay therapy should not be initiated if the patient has a history of liver disease or exhibits clinical evidence of active liver disease, cirrhosis, hepatitis, history of alcohol abuse or increased serum transaminase levels (ALT >1.5 times the upper limit of normal).

WARNINGS

SEE BOXED WARNING.

PRECAUTIONS

General

Because of its mechanism of action, Prelay is active only in the presence of insulin. Therefore, Prelay should not be used in type 1 diabetes or for the treatment of diabetic keto-acidosis.

Hypoglycemia: Patients receiving Prelay in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia and a reduction in the dose of the concomitant agent may be necessary. Hypoglycemia has not been observed during the administration of Prelay as as a single agent and would not be expected based on the mechanism of action.

Ovulation: In premenopausal anovulatory patients with insulin resistance, Prelay treatment may result in resumption of ovulation. **These patients may be at risk for pregnancy.**

Hematologic: Across all clinical studies, hemoglobin declined by 3 to 4 % in troglitazone-treated patients compared with 1 to 2% in those treated with placebo. White blood cell counts also declined slightly in troglitazone-treated patients compared to those treated with placebo. These changes occurred within the first four to eight weeks of therapy. Levels stabilized and remained unchanged for up to two years of continuing therapy. These changes may be due to the dilutional effects of increased plasma volume and have not been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Laboratory Abnormalities).

Use in Patients With Heart Failure

Heart enlargement without microscopic changes has been observed in rodents at exposures of parent compound and active metabolite exceeding 7 times the AUC of the 400-mg human dose (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility, and Animal Toxicology). Serial echocardiographic evaluations in monkeys treated chronically at exposures at 4-9 times the human exposure to parent compound and active metabolite at the 400-mg dose did not reveal changes in heart size or function. In a 2-year echocardiographic clinical study using 600 to 800 mg/day of Prelay in patients with type 2 diabetes, no increase in left ventricular mass or decrease in cardiac output was observed. The methodology employed was able to detect a change of about 10% or more in left ventricular mass.

In animal studies, troglitazone treatment was associated with increases of 6% to 15% in plasma volume. In a study of 24 normal volunteers, an increase in plasma volume of 6% to 8% compared to placebo was observed following 6 weeks of troglitazone treatment.

No increased incidence of adverse events potentially related to volume expansion (e.g., congestive heart failure) have been observed during controlled clinical trials. However, patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials. Therefore, Prelay is not indicated unless the expected benefit is believed to outweigh the potential risk to patients with NYHA Class III or IV cardiac status.

Information for Patients

Prelay should be taken with meals. If the dose is missed at the usual meal, it may be taken at the next meal. If the dose is missed on one day, the dose should not be doubled the following day.

It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. During periods of stress such as fever, trauma, infection, or surgery, insulin requirements may change and patients should seek the advice of their physician.

Patients who develop nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine or other symptoms suggestive of hepatic dysfunction or jaundice should immediately report these signs or symptoms to their physician. Patients should be informed that blood will be drawn to check their liver function at the start of therapy, monthly for the first year of therapy, and quarterly thereafter. (See Patient Information.)

When using Prelay with insulin, metformin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Use of Prelay can cause resumption of ovulation in women taking oral contraceptives and in patients with polycystic ovary disease. Therefore, a higher dose of an oral contraceptive or an alternative method of contraception should be considered.

Prelay may affect other medications used in diabetic patients. Patients started on Prelay should ask their physician to review their other medications to make sure that they are not affected by Prelay.

Drug Interactions

Oral Contraceptives: Administration of Prelay with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%, which could result in loss of contraception. Therefore, a higher dose of oral contraceptive or an alternative method of contraception should be considered.

Terfenadine: Coadministration of Prelay with terfenadine decreases the plasma concentration of both terfenadine and its active metabolite by 50-70% and may result in decreased efficacy of terfenadine.

Cholestyramine: Concomitant administration of cholestyramine with Prelay reduces the absorption of troglitazone by 70%; thus, coadministration of cholestyramine and Prelay is not recommended.

Glyburide: Coadministration of Prelay and glyburide does not appear to alter troglitazone or glyburide pharmacokinetics.

Digoxin: Coadministration of Prelay with digoxin does not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Prelay has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Acetaminophen: Coadministration of acetaminophen and Prelay does not alter the pharmacokinetics of either drug.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in Prelay-treated patients with type 2 diabetes mellitus.

The above interactions with terfenadine and oral contraceptives suggest that troglitazone may induce drug metabolism by CYP3A4. Studies have not been performed with other drugs metabolized by this enzyme such as: astemizole, calcium channel blockers, cisapride, corticosteroids, cyclosporine, HMG-CoA reductase inhibitors, tacrolimus, triazolam, and trimetrexate. The possibility of altered safety and efficacy should be considered when Prelay is used concomitantly with these drugs.

Patients stable on one or more of these agents when Prelay is started should be closely monitored and their therapy adjusted as necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Troglitazone was administered daily for 104 weeks to male rats at 100, 400, or 800 mg/kg and to female rats at 25, 50, or 200 mg/kg. No tumors of any type were increased at the low and mid doses. Plasma drug exposure based on AUC of parent compound and total metabolites at the low and mid doses was up to 24-fold higher than human exposure at 400 mg daily. The highest dose in each sex exceeded the maximum tolerated dose. In a 104-week study in mice given 50, 400, or 800 mg/kg, incidence of hemangiosarcoma was increased in females at 400 mg/kg and in both sexes at 800 mg/kg; incidence of hepatocellular carcinoma was increased in females at 800 mg/kg. The lowest dose associated with increased tumor incidence (400 mg/kg) was associated with AUC values of parent compound and total metabolites that were at least 2-fold higher than the human exposure at 400 mg daily. No tumors of any type were increased in mice at 50 mg/kg at exposures up to 40% of that in humans at 400 mg daily, based on AUC of parent compound and total metabolites.

Troglitazone was neither mutagenic in bacteria nor clastogenic in bone marrow of mice. Equivocal increases in chromosome aberrations were observed in an *in vitro* Chinese hamster lung cell assay. In mouse lymphoma cell gene mutations assays, results were equivocal when conducted with a microtiter technique and negative with an agar plate technique. A liver unscheduled DNA synthesis assay in rats was negative.

No adverse effects on fertility or reproduction were observed in male or female rats given 40, 200, or 1000 mg/kg daily prior to and throughout mating and gestation. AUC of parent compound at these doses was estimated to be 3- to 9-fold higher than the human exposure.

Animal Toxicology

Increased heart weights without microscopic changes were observed in mice and rats treated for up to 1 year at exposure (AUC) of parent and active metabolite exceeding 7 times the human AUC at 400 mg/day. These heart weight increases were reversible

in 2- and 13-week studies, were prevented by coadministration of an ACE inhibitor, and 14 days of troglitazone administration to rats did not affect left ventricular performance. In the lifetime carcinogenicity studies, microscopic changes were noted in the hearts of rats but not in mice. In control and treated rats, microscopic changes included myocardial inflammation and fibrosis and karyomegaly of atrial myocytes. The incidence of these changes in drug-treated rats was increased compared to controls at twice the AUC of the 400 mg human dose.

Pregnancy

Pregnancy Category B. Troglitazone was not teratogenic in rats given up to 2000 mg/kg or rabbits given up to 1000 mg/kg during organogenesis. Compared to human exposure of 400 mg daily, estimated exposures in rats (parent compound) and rabbits (parent compound and active metabolite) based on AUC at these doses were up to 9-fold and 3-fold higher, respectively. Body weights of fetuses and offspring of rats given 2000 mg/kg during gestation were decreased. Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats given 40, 200, or 1000 mg/kg during late gestation and lactation periods; no effects were observed in offspring of rats given 10 or 20 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Prelay should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

It is not known whether troglitazone is secreted in human milk. Troglitazone is secreted in the milk of lactating rats. Because many drugs are excreted in human milk, Prelay should not be administered to a breast-feeding woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Twenty-two percent of patients in clinical trials of Prelay were 65 and over. No differences in effectiveness and safety were observed between these patients and younger patients.

ADVERSE REACTIONS

Two patients in the clinical studies developed reversible jaundice; one of these patients had a liver biopsy which was consistent with an idiosyncratic drug reaction. An additional patient had a liver biopsy which was also consistent with an idiosyncratic drug reaction. Symptoms that are associated with hepatic dysfunction have been reported, including: nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine, abnormal liver function tests (including increased ALT, AST, LDH, alkaline phosphatase, bilirubin). Also see WARNINGS.

The overall incidence and types of adverse reactions reported in placebo-controlled clinical trials for Prelay-treated patients and placebo-treated patients are shown in Table 6. In patients treated with Prelay in glyburide-controlled studies (N=550) or uncontrolled studies (N=510), the safety profile of Prelay appeared similar to that displayed in Table 6. The incidence of withdrawals during clinical trials was similar for patients treated with placebo or Prelay (4%).

TABLE 6. North American Placebo-Controlled Clinical Studies: Adverse Events Reported at a Frequency ≥5% of Prelay-Treated Patients

	% of Patients	
	Placebo N=492	Prelay N=1450
Infection	22	18
Headache	11	11
Pain	14	10
Accidental Injury	6	8
Asthenia	5	6
Dizziness	5	6
Back Pain	4	6
Nausea	4	6
Rhinitis	7	5
Diarrhea	6	5
Urinary Tract Infection	6	5
Peripheral Edema	5	5
Pharyngitis	4	5

Laboratory Abnormalities

Hematologic: Small decreases in hemoglobin, hematocrit, and neutrophil counts (within the normal range) were more common in Prelay-treated than placebo-treated patients and may be related to increased plasma volume observed with Prelay treatment. Hemoglobin decreases to below the normal range occurred in 5% of Prelay-treated and 4% of placebo-treated patients.

Lipids: Small changes in serum lipids have been observed (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

Serum Transaminase Levels: During all clinical studies in North America, a total of 48 of 2510 (1.9%) Prelay-treated patients and 3 of 475 (0.6%) placebo-treated patients had ALT levels greater than 3 times the upper limit of normal. Nineteen patients (0.8%) had ALT over 8x ULN, 5 patients (0.2%) had ALT values over 30x ULN. Twenty of the Prelay-treated and one of the placebo-treated patients were withdrawn from treatment. Two of the 20 Prelay-treated patients developed reversible jaundice; one of these patients had a liver biopsy which was consistent with an idiosyncratic drug reaction. An additional Prelay-treated patient had a liver biopsy which was also consistent with an idiosyncratic drug reaction. (See ADVERSE REACTIONS, Laboratory Abnormalities.)

Postintroduction Reports

Adverse events associated with Prelay that have been reported since market introduction, that are not listed above, and for which causal relationship to drug has not been established include the following: congestive heart failure, weight gain, edema, fever, abnormal lab tests including increased CPK and creatinine, hyperglycemia, syncope, anemia, malaise.

Decreased cyclosporine concentrations have been reported with concomitant use of troglitazone.

DOSAGE AND ADMINISTRATION

Prelay should be taken with a meal.

Combination Therapy

Sulfonylureas: Prelay in combination with a sulfonylurea should be initiated at 200 mg once daily. The current sulfonylurea dose should be continued upon initiation of Prelay therapy. For patients not responding adequately, the Prelay dose should be increased at 2 to 4 weeks. The maximum recommended dose is 600 mg once daily. The dose of sulfonylurea may require lowering to optimize therapy.

Metformin: For patients not responding to metformin therapy or metformin and sulfonylureas, 400 mg daily of Prelay may be added.

Insulin: The current insulin dose should be continued upon initiation of Prelay therapy. Prelay therapy should be initiated at 200 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of Prelay should be increased after approximately 2 to 4 weeks. The usual dose of Prelay is 400 mg once daily. The maximum recommended daily dose is 600 mg. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and Prelay. Further adjustments should be individualized based on glucose-lowering response.

Patients With Renal Insufficiency

Dose adjustment in patients with renal insufficiency is not required (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism). Out of 2938 patients 148 (5%) had a serum creatinine ≥1.5 at baseline. Of these 148 patients, 145 had creatinine levels between 1.5 and 2.0, inclusive; only 3 patients had levels > 2.0. No consistent trend was seen in any of these adverse events, and no worsening of renal insufficiency was observed.

Patients With Hepatic Impairment

Prelay therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >1.5 times the upper limit of normal). See CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency and WARNINGS.

HOW SUPPLIED

Prelay is available in 200-. 300- and 400-mg tablets as follows:

200-mg Tablets: Yellow, oval, non-scored, film-coated tablet with PD 352 debossed on one side, and 200 on the other, available in:

N 0000-0000-00 Bottles of 30
N 0000-0000-00 Bottles of 90
N 0000-0000-00 (10 × 10 unit-dose blisters)

300 mg Tablets: White, oval, non-scored, film-coated tablet with PD 357 debossed on one side and 300 on the other, available in:

N 0000-0000-00 Bottles of 60
N 0000-0000-00 Bottles of 120
N 0000-0000-00 40 unit-dose blisters

400-mg Tablets: Tan, oval, non-scored, film-coated tablet with PD 353 debossed on one side, and 400 on the other, available in:

N 0000-0000-00 Bottles of 30
N 0000-0000-00 Bottles of 90
N 0000-0000-00 (10 × 10 unit-dose blisters)

Storage

Store at controlled room temperature, 20° C to 25° C (68° F-77° F). Protect from moisture and humidity.

Rx Only

September 1999

Sankyo U. S. A. Corporation
New York, N.Y.

APPEARS THIS WAY ON ORIGINAL

Manufactured by:
Parke Davis
Pharmaceuticals. Ltd.
Vega Baja, PR 00694

Distributed by:
PARKE-DAVIS
Div of Warner-Lambert Co.
Morris Plains, NJ 07950 USA

Marketed by:
PARKE-DAVIS
Div of Warner-Lambert Co. and
SANKYO PARKE DAVIS
Parsippany, NJ 07054 USA

PATIENT INFORMATION

Prelay® (Pre-lay)
TROGLITAZONE
200, 300, AND 400 MG TABLETS

What is the most important information I should know about Prelay?

Serious liver problems have occurred in some people who have taken Prelay. These problems are generally reversible. However, for some people, these problems have cause liver failure, resulting in liver transplant or death.

Your doctor will test your blood before you start taking Prelay to see if your liver is normal. You will have this blood test every month during your first year of therapy to see if Prelay is affecting your liver. The test will be give 4 times a year after the first year. Your doctor may ask you to have these tests more often to follow up on abnormal results. Your doctor may also order other tests. **IT IS VERY IMPORTANT THAT YOU HAVE THESE BLOOD TESTS and follow your doctor's instructions.** These tests cannot completely eliminate the possibility of your having a serious liver problem. However, they may help reduce your risk.

STOP TAKING PRELAY and call your doctor right away if you have:

- **Jaundice (yellowing of the skin or whites of the eyes)**
- **Brown urine**

If you have signs of possible liver disease, call your doctor right away. Such signs include:

- Nausea
- Vomiting
- Stomach or abdominal pain
- Fatigue (feeling extremely tired)
- Lack of appetite

What is Prelay?

Prelay, when used in combination with diet, exercise, or other diabetes medicines treats type 2 diabetes. Type 2 diabetes is also called non-insulin dependent diabetes mellitus (NIDDM), or adult-onset diabetes.

People with type 2 diabetes either can't make enough insulin or can't adequately use the insulin that their body makes (insulin resistance). As a result, sugar (glucose) builds up in their blood. This buildup can cause serious medical problems such as nerve damage, kidney damage, eye disease, heart disease, tooth and gum disease, and infections. Prelay, when used in combination with diet, exercise, and other diabetes medicines, lowers blood sugar by improving the way your body uses insulin. Prelay decreases insulin resistance that occurs when the body can't adequately use the insulin that it makes. By decreasing insulin resistance, Prelay helps the insulin in your body get sugar (glucose) from your blood into your muscle and fat cells where it is used as energy. Prelay does not cause your body to make more insulin.

Medical research has shown that Prelay, used in combination with diet, exercise and other diabetes medicines, can help you control your glucose.

IMPORTANT: When taking Prelay, controlling your weight and getting regular exercise are important parts of your treatment.

Who should not take Prelay?

You should not take Prelay if you have a history of liver disease or have signs of active liver disease such as cirrhosis or hepatitis, or if you have a history of heavy alcohol drinking. If you have any of these, tell your doctor **right away**. You also should not take Prelay if you have an allergy to Prelay or any of its ingredients.

How should I take Prelay?

Take Prelay once a day with a meal. Your doctor will tell you how much to take. If you forget to take your Prelay dose at the usual meal, take it at the next meal that same day. If you

completely forget to take it one day, skip the missed dose. **Never take more than the usual amount of Prelay in one day to make up for a missed dose.** If you take more than the usual amount, contact your doctor right away.

What should I avoid while taking Prelay?

Prelay has not been tested in patients with sever heart failure. Prelay may cause you to retain fluid. Fluid retention may cause serious problems in patients with heart failure. If you know you have heart failure, consult your doctor before taking Prelay.

Prelay makes some birth control pills less effective. If you are taking birth control pills, you may need a higher dose birth control pill or another birth control method. Ask your doctor. Women who have not reached menopause and have not been ovulating may be at risk for becoming pregnant while taking Prelay.

Prelay may interfere with the way some drugs work. Some drugs may interfere with the action of Prelay. For this reason, it is important to tell your doctor about all drugs you take, including over-the-counter (non-prescription) medicines, and dietary supplements. You should also tell your doctor about your alcohol use, and eating and exercise habits, as wells as all of your past or present medical conditions or problems.

What are the possible or reasonably likely side effects of Prelay?

See the discussion of serious liver problems in the section "What is the most important information I should know about Prelay?" Prelay, like all medicines used to lower blood sugar, can cause side effects in some patients. The most common side effects seen in patients taking Prelay in medical studies were headache, infection and pain. These symptoms were seen just as often in patients taking a pill without the medicine in it (placebo). Prelay may also cause weight gain.

When you take Prelay in combination with insulin or with another diabetes medicine, your blood sugar may be reduced too much (low blood sugar). Talk with your doctor about this possibility. You should check your blood sugar levels on a regular schedule and be aware of the symptoms of low blood sugar. The most common symptoms of low blood sugar include dizziness, sweating, unusual hunger, shakiness, and a very rapid heartbeat.

Medicines are sometimes prescribed for purposes other than those listed in this Patient Information sheet. You should not use Prelay for a condition for which it was not prescribed. Do not give your Prelay to anyone else. Consult your healthcare provider about any concerns you have about the use of Prelay or your type 2 diabetes. Your healthcare provided or Sankyo USA can give you a more detailed leaflet about Prelay that is written for healthcare professionals. (For further information call Sankyo USA at 1-XXX-XXX-XXXX.)

Rx Only
August 1999

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Vega Baja, PR 00694

Distributed by:
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Morris Plains, NJ 07950 USA

Marketed by:
PARKE-DAVIS
Div of Warner-Lambert Co. and
SANKYO PARKE DAVIS
Parsippany, NJ 07054 USA

This Patient Information has been approved by the U.S. Food and Drug Administration.

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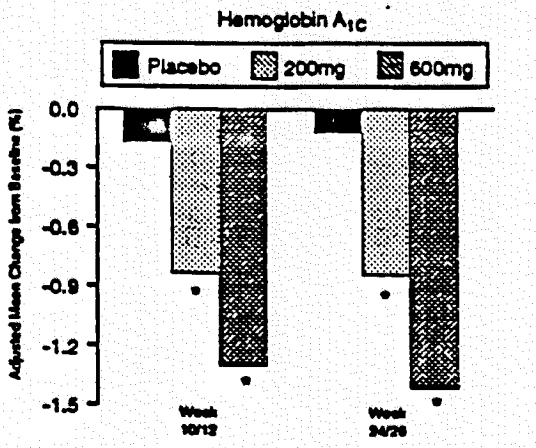

FIGURE 1

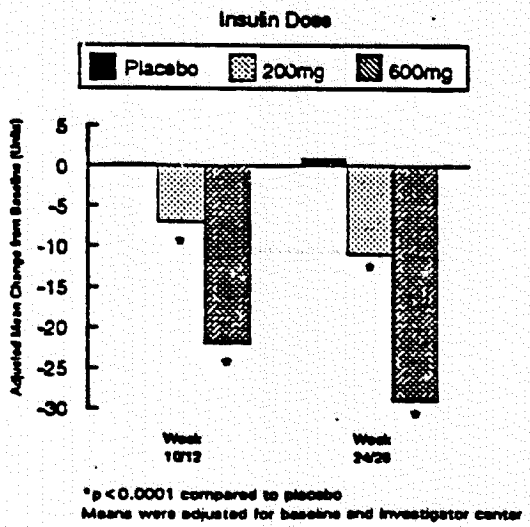

FIGURE 2