Rezulin®
(Troglitazone) Tablets

WARNINGS

Hepatic

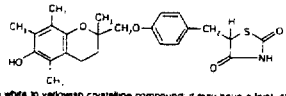
Rare cases of severe idiosyncratic hepatocellular injury have been reported during marketed use (see ADVERSE REACTIONS). The hepatic injury is usually reversible, but very rare cases of hepatic failure, leading to death or liver transplant, have been reported. Injury has occurred after both short- and long-term troglitazone treatment.

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 Twenty of the Rezulin-treated and one of the placebo-treated patients were withdrawn from treatment.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

Serum transaminase levels should be checked at the start of therapy, monthly for the first eight months of therapy, every two months for the remainder of the first year of Rezulin therapy, and periodically thereafter. Rezulin 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). Liver function tests also should be obtained for patients at the first symptoms suggestive of hepatic dysfunction, eg, nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine. If serum transaminase levels are moderately increased (ALT>1.5 to 2 times the upper limit of normal), liver function tests should be repeated within a week and then weekly until the level returns to normal. If at any time a patient has jaundice or ALT rises above 3 times the upper limit of normal, Rezulin should be discontinued.

DESCRIPTION

Rezulin® (troglitazone) is an oral antihyperglycemic agent which acts primarily by decreasing insulin resistance. Rezulin is used in the management of type II diabetes (non-insulin-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 $C_{24}H_{19}NO_5S$ 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.

Rezulin 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 (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 II 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 regenerulation 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 800 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·h/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)
800	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 Rezulin 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 II diabetes. Steady-state levels of Metabolite 1 are 8 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 66% of the radioactivity is recovered in feces (65%) 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, Rezulin 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 [illegible] 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 Rezulin improves insulin sensitivity in insulin-resistant patients. Rezulin increases insulin-dependent glucose disposal, reduces hepatic gluconeogenesis, and enhances cellular responsiveness to insulin and thus improves dysfunctional glucose homeostasis. In patients with type II diabetes, the decreased insulin resistance produced by Rezulin causes decreases in serum glucose, plasma insulin, and hemoglobin A_{1C}. Unlike sulfonylureas, Rezulin does not stimulate insulin secretion. Addition of Rezulin to a sulfonylurea has a synergistic effect since both agents act to improve glucose tolerance by different but complementary mechanisms. These effects occur without weight loss and persist for 52 weeks of Rezulin treatment.

In clinical trials of Rezulin as monotherapy or in combination, an increase in LDL (up to 13%), HDL (up to 18%), 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. Patients treated with Rezulin as monotherapy or in combination with other agents exhibited a reduction in fasting (-13% to -28%) and postprandial triglyceride levels. For patients on Rezulin and insulin, reduction in insulin doses may occur following Rezulin 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.

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

Clinical Studies

Combination With Sulfonylureas

A 52-week, double-blind, placebo-controlled study of Rezulin and 12 mg micronized glyburide alone and in combination, was conducted in patients with type II 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. Patients randomized to receive micronized glyburide showed mean increases in FSG and HbA_{1C}. Similarly, patients who switched from a sulfonylurea to Rezulin monotherapy also demonstrated increases in FSG and HbA_{1C}.

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

	200 mg Rezulin + Glyburide	400 mg Rezulin + Glyburide	600 mg Rezulin + Glyburide
FSG (mg/dL)			
Mean Baseline	226	231	220
Adjusted Mean Change From Baseline	-31	-38	-55
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 (1 yr)

Rezulin (mg)	0	200	400	600
Glyburide (mg)	12	12	12	12
HbA_{1C} (%)				
≤7%	1	22	21	41
≤8%	10	33	33	50

A combination of 200, 400, or 600 mg of Rezulin 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 Insulin

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

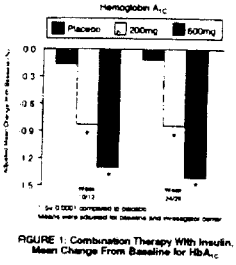
In one 6-month, double-blind, placebo-controlled study in insulin-treated type II diabetic patients receiving a mean of 73 (range 27-143) units/day of insulin with a mean baseline HbA_{1C} of 9.4% (range 7.04-12.48), Rezulin (200 or 600 mg/day) or placebo was added to the insulin therapy. Investigators were instructed to reduce insulin doses only if two consecutive FSGs were <100 mg/dL. Rezulin-treated patients showed a significant (p<0.0001) reduction in HbA_{1C} compared with patients who received placebo (see Table 4).

Thirty percent of patients treated with 200 mg Rezulin and 57% of patients treated with 600 mg Rezulin 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 Rezulin treatment group and 42% in the 600 mg Rezulin treatment group compared with 1% in the placebo group. HbA_{1C} values and insulin dose as a function of duration of Rezulin treatment are presented in Figures 1 and 2.

TABLE 4. Combination Therapy with Insulin: Mean Change From Baseline at 6 Months

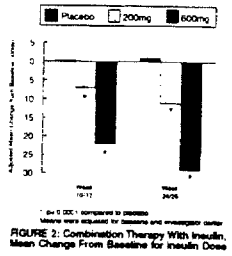
Parameter	Placebo	Troglitazone	
		200 mg	600 mg
N	118	116	118
HbA_{1C} (%)			
Mean Baseline (SE)	9.43 (0.10)	9.51 (0.10)	9.32 (0.11)
Mean Change From Baseline (SE)†	-0.12 (0.10)	-0.84 (0.10)	-1.41 (0.10)
Adjusted Mean Difference From Placebo (SE)	-	-0.72 (0.14)*	-1.29 (0.14)*
Percent Mean Change From 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 ≤0.0001
†Least squares mean adjusted for investigator center and baseline.



* p< 0.0001 compared to placebo
Means were adjusted for baseline and investigator center

FIGURE 1: Combination Therapy With Insulin, Mean Change From Baseline for HbA_{1C}



* p< 0.001 compared to placebo
Means were adjusted for baseline and investigator center

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 II diabetics who previously were poorly controlled on oral agents receiving 30 to 150 units insulin/day assessed the use of Rezulin 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) Rezulin 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 Rezulin 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

Monotherapy

Three clinical trials, including 2 placebo-controlled studies with durations from 12 to 26 weeks have been conducted to study the use of Rezulin as monotherapy. These studies have examined Rezulin doses from 100 to 600 mg/day in approximately 1500 patients. The patients studied have included patients previously treated with a sulfonylurea who were studied following prior therapy wash out (N=1265) and patients previously treated with diet only (N=230). In patients previously treated with a sulfonylurea, Rezulin treatment did not result in an improvement in glycemic control beyond that seen with the patients' prior therapy, although glucose lowering was significantly better than that seen with placebo treatment. For patients previously treated with diet, Rezulin doses of 200 mg, 400 mg and 600 mg/day were associated with improved FSG compared to placebo. However, only the 600 mg/day dose resulted in a difference compared with placebo that was statistically significant in both studies (see Table 5). At 600 mg per day, 58% of patients previously treated with diet in the 12 week study and 47% of patients previously treated with diet in the 26-week study (versus placebo values of 28% and 21%, respectively) had a response to Rezulin of ≥ 30 mg/dL reduction from baseline in fasting serum glucose.

TABLE 5. Glycemic Parameters in Diet-Failure Patients

	12 Week Study			
	Placebo	200	400	600
N	19	23	20	33
FSG (mg/dL)				
Mean Baseline	168	169	161	196
Adjusted Mean Change From Baseline	14	-14	-20	-38
Adjusted Mean Difference From Placebo		-31*	-37*	-55*
HbA_{1c} (%)				
Mean Baseline	8	8.2	8.5	8.5
Adjusted Mean Change From Baseline	-0.1	-0.6	-0.6	-0.8
Adjusted Mean Difference From Placebo		-0.5	-0.6	-0.7*

	26 Week Study			
	Placebo	200	400	600
N	18	18	19	15
FSG (mg/dL)				
Mean Baseline	202	191	201	201
Adjusted Mean Change From Baseline	6	-24	-17	-46
Adjusted Mean Difference From Placebo		-18	-10	-42*
HbA_{1c} (%)				
Mean Baseline	8.7	8.3	8.5	8.6
Adjusted Mean Change From Baseline	0.4	-0.2	0.3	-1
Adjusted Mean Difference From Placebo		-0.6	-0.1	-1.4*

*p<0.05

INDICATIONS AND USAGE

Rezulin may be used concomitantly with a sulfonylurea or insulin to improve glycemic control. Rezulin as monotherapy is indicated as an adjunct to diet and exercise to lower blood glucose in patients with type II diabetes (see DOSAGE AND ADMINISTRATION). Rezulin should not be used as monotherapy in patients previously well-controlled on sulfonylurea therapy. For patients inadequately controlled with a sulfonylurea alone, Rezulin should be added to, not substituted for, the sulfonylurea.

Management of type II diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient. This is important not only in the primary treatment of type II diabetes, but in maintaining the efficacy of drug therapy. Prior to initiation of Rezulin therapy, secondary causes of poor glycemic control, eg, infection or poor injection technique, should be investigated and treated.

CONTRAINDICATIONS

Rezulin is contraindicated in patients with known hypersensitivity or allergy to Rezulin or any of its components.

WARNINGS

SEE BOXED WARNING.

PRECAUTIONS

General

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

Hypoglycemia: Patients receiving Rezulin 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 Rezulin as monotherapy and would not be expected based on the mechanism of action.

Ovulation: In premenopausal anovulatory patients with insulin resistance, Rezulin 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, then 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 Rezulin in patients with type II 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 8 weeks of troglitazone treatment.

No increased incidence of adverse events potentially related to volume expansion (eg, 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, Rezulin 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

Rezulin 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 eight months of therapy, every two months for the remainder of the first year of Rezulin therapy, and periodically thereafter.

When using combination therapy with insulin 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 Rezulin 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.

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

Drug Interactions

Oral Contraceptives: Administration of Rezulin 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 Rezulin 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 Rezulin reduces the absorption of troglitazone by 70%, thus, coadministration of cholestyramine and Rezulin is not recommended.

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

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

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

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

Metformin: No information is available on the use of Rezulin with metformin.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in Rezulin-treated patients with type II 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. (See ADVERSE REACTIONS, Postintroduction Reports.) The possibility of altered safety and efficacy should be considered when Rezulin is used concomitantly with these drugs.

Patients stable on one or more of these agents when Rezulin 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 chromosomal 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 katty-omegaly 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. Rezulin 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, Rezulin 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 Rezulin 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 or hepatitis have been reported rarely: 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 Rezulin-treated patients and placebo-treated patients are shown in Table 6. Patients treated with Rezulin in glyburide-controlled studies (N=550) or uncontrolled studies (N=510); the safety profile of Rezulin appeared similar to that displayed in Table 6. The withdrawal rate for drug was during clinical trials was similar for patients treated with placebo (4%) and Rezulin (4%).

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

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

Types of adverse events seen when Rezulin was used concomitantly with insulin (N=541) were similar to those during Rezulin monotherapy (N=1731), although hypoglycemia occurred more frequently in insulin combination therapy (see PRECAUTIONS).

Laboratory Abnormalities

Hematologic: Small decreases in hemoglobin, hematocrit, and neutrophil counts (within the normal range) were more common in Rezulin-treated than placebo-treated patients and may be related to increased plasma volume observed with Rezulin treatment. Hemoglobin decreased to below the lower limit of normal in 0.8% of Rezulin-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 trials, a total of 48 of 2416 (1.9%) Rezulin-treated patients and 3 of 475 (0.6%) placebo-treated patients had ALT levels greater than 3 times the upper limit of normal. During controlled clinical trials, 2% of Rezulin-treated patients had reversible elevations in AST or ALT greater than 3 times the upper limit of normal, compared with 0.6% of patients receiving placebo. Hyperbilirubinemia (>1.5 x upper limit of normal) was found in 0.7% of Rezulin-treated patients compared with 1.5% of patients receiving placebo. In the population of patients treated with Rezulin, mean and median values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline, while values for LDH were increased slightly (see WARNINGS).

Postintroduction Reports

Adverse events associated with Rezulin 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

Rezulin should be taken with a meal.

Combination Therapy

Sulfonylureas: Rezulin in combination with a sulfonylurea should be initiated at 200 mg once daily. The current sulfonylurea dose should be continued upon initiation of Rezulin therapy. For patients not responding adequately, the Rezulin 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.

Insulin: The current insulin dose should be continued upon initiation of Rezulin therapy. Rezulin therapy should be initiated at 200 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of Rezulin should be increased after approximately 2 to 4 weeks. The usual dose of Rezulin 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 Rezulin. Further adjustments should be individualized based on glucose-lowering response.

Monotherapy

Rezulin monotherapy in patients not adequately controlled with diet alone should be initiated at 400 or 600 mg once daily. For patients not responding to 400 mg once daily, the Rezulin dose should be increased to 600 mg after one month. For patients not responding adequately to 600 mg after one month, Rezulin should be discontinued and alternative therapeutic options should be pursued. See CLINICAL PHARMACOLOGY, Clinical Studies, Monotherapy.

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; of these, 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

Rezulin 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

Rezulin 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 0071-0352-15 Bottles of 30 N 0071-0352-23 Bottles of 90
N 0071-0352-40 (10 x 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 0071-0357-20 Bottles of 60 N 0071-0357-25 Bottles of 120

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 0071-0353-15 Bottles of 30 N 0071-0353-23 Bottles of 90
N 0071-0353-40 (10 x 10 unit-dose blisters)

Storage

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

Rx only

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