AA:LX

PRESCRIBING INFORMATION

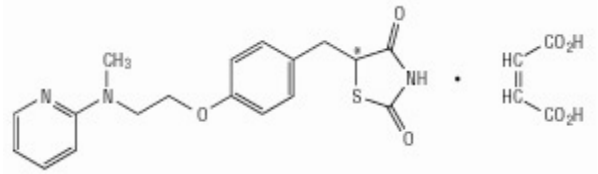
AVANDARYL™

(rosiglitazone maleate and glimepiride)
Tablets

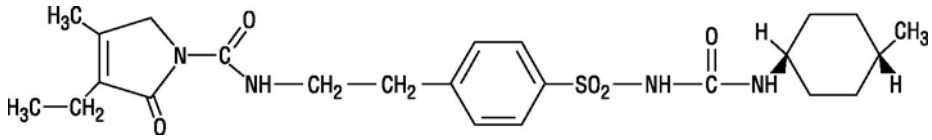
DESCRIPTION

AVANDARYL (rosiglitazone maleate and glimepiride) tablets contain 2 oral antidiabetic drugs used in the management of type 2 diabetes: Rosiglitazone maleate and glimepiride.

Rosiglitazone maleate is an oral antidiabetic agent of the thiazolidinedione class which acts primarily by increasing insulin sensitivity. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors. Chemically, rosiglitazone maleate is (±)-5-[[4-[2-(methyl-2-pyridinylamino) ethoxy]phenyl] methyl]-2,4-thiazolidinedione, (Z)-2-butenedioate (1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the enantiomers are functionally indistinguishable. The molecular formula is $C_{18}H_{19}N_3O_3S•C_4H_4O_4$. Rosiglitazone maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pK_a values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range. The structural formula of rosiglitazone maleate is:



Glimepiride is an oral antidiabetic drug of the sulfonylurea class. Glimepiride is a white to yellowish-white, crystalline, odorless to practically odorless powder. Chemically, glimepiride is 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea with a molecular weight of 490.62. The molecular formula for glimepiride is $C_{24}H_{34}N_4O_5S$. Glimepiride is practically insoluble in water. The structural formula of glimepiride is:



AVANDARYL is available for oral administration as tablets containing a fixed dose of 4 mg rosiglitazone with variable doses of glimepiride (1, 2, or 4 mg) in a single tablet formulation: 4 mg rosiglitazone with 1 mg glimepiride (4 mg/1 mg), 4 mg rosiglitazone with 2 mg glimepiride (4 mg/2 mg), and 4 mg rosiglitazone with 4 mg glimepiride (4 mg/4 mg). In addition, each tablet contains the following inactive ingredients: Hypromellose 2910, lactose monohydrate, macrogol (polyethylene glycol), magnesium stearate, microcrystalline cellulose, sodium starch glycolate, titanium dioxide, and 1 or more of the following: Yellow, red, or black iron oxides.

CLINICAL PHARMACOLOGY

Mechanism of Action: AVANDARYL combines 2 antidiabetic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: Rosiglitazone maleate, a member of the thiazolidinedione class, and glimepiride, a member of the sulfonylurea class. Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas sulfonylureas act primarily by stimulating release of insulin from functioning pancreatic beta cells.

Rosiglitazone improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPARγ-responsive genes also participate in the regulation of fatty acid metabolism.

Insulin resistance is a common feature characterizing the pathogenesis of type 2 diabetes. The antidiabetic activity of rosiglitazone has been demonstrated in animal models of type 2 diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. Rosiglitazone reduces blood glucose concentrations and reduces hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse, and fa/fa fatty Zucker rat.

In animal models, the antidiabetic activity of rosiglitazone was shown to be mediated by increased sensitivity to insulin's action in the liver, muscle, and adipose tissues. The expression of the insulin-regulated glucose transporter GLUT-4 was increased in adipose tissue. Rosiglitazone did not induce hypoglycemia in animal models of type 2 diabetes and/or impaired glucose tolerance.

The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of sulfonylureas such as glimepiride. This is supported by both preclinical and clinical studies demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These findings are consistent with the results of a long-term, randomized, placebo-controlled trial in which glimepiride therapy improved postprandial insulin/C-peptide responses and overall glycemic control without producing clinically meaningful increases in fasting insulin/C-peptide levels. However, as with other sulfonylureas, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established.

Pharmacokinetics: In a bioequivalence study of AVANDARYL 4 mg/4 mg, the area under the curve (AUC) and maximum concentration (C_{max}) of rosiglitazone following a single dose of the combination tablet were bioequivalent to rosiglitazone 4 mg concomitantly administered with glimepiride 4 mg under fasted conditions. The AUC of glimepiride following a single fasted 4 mg/4 mg dose was equivalent to glimepiride concomitantly administered with rosiglitazone, while the C_{max} was 13% lower when administered as the combination tablet (see Table 1).

Table 1. Pharmacokinetic Parameters for Rosiglitazone and Glimepiride (n = 28)

	Rosiglitazone		Glimepiride	
Parameter (Units)	**Regimen A**	**Regimen B**	**Regimen A**	**Regimen B**
$AUC_{0\text{-}inf}$ (ng.hr/mL)	1,259 (833-2,060)	1,253 (756-2,758)	1,052 (643-2,117)	1,101 (648-2,555)
$AUC_{0\text{-}t}$ (ng.hr/mL)	1,231 (810-2,019)	1,224 (744-2,654)	944 (511-1,898)	1,038 (606-2,337)
C_{max} (ng/mL)	257 (157-352)	251 (77.3-434)	151 (63.2-345)	173 (70.5-329)
$T_{½}$ (hr)	3.53 (2.60-4.57)	3.54 (2.10-5.03)	7.63 (4.42-12.4)	5.08 (1.80-11.31)
T_{max} (hr)	1.00 (0.48-3.02)	0.98 (0.48-5.97)	3.02 (1.50-8.00)	2.53 (1.00-8.03)

AUC = area under the curve; C_{max} = maximum concentration; $T_{½}$ = terminal half-life; T_{max} = time of maximum concentration.

Regimen A = AVANDARYL 4 mg/4 mg tablet; Regimen B = Concomitant dosing of a rosiglitazone 4 mg tablet AND a glimepiride 4 mg tablet.

Data presented as geometric mean (range), except $T_{½}$ which is presented as arithmetic mean (range) and T_{max}, which is presented as median (range).

The rate and extent of absorption of both the rosiglitazone component and glimepiride component of AVANDARYL when taken with food were equivalent to the rate and extent of absorption of rosiglitazone and glimepiride when administered concomitantly as separate tablets with food.

Absorption: The AUC and C_{max} of glimepiride increased in a dose-proportional manner following administration of AVANDARYL 4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg. Administration of AVANDARYL in the fed state resulted in no change in the overall exposure of rosiglitazone; however, the C_{max} of rosiglitazone decreased by 32% compared to the fasted state. There was an increase in both AUC (19%) and C_{max} (55%) of glimepiride in the fed state compared to the fasted state.

Rosiglitazone: The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing. The C_{max} and AUC of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range.

Glimepiride: After oral administration, glimepiride is completely (100%) absorbed from the gastrointestinal tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with type 2 diabetes have shown significant absorption of glimepiride within 1 hour after administration and C_{max} at 2 to 3 hours.

Distribution: Rosiglitazone: The mean (CV%) oral volume of distribution (V_{ss}/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

Glimepiride: After intravenous (IV) dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metabolism and Excretion: Rosiglitazone: Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone. In vitro data demonstrate that rosiglitazone is predominantly metabolized by cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway. Following oral or IV administration of [^{14}C]rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [^{14}C]related material ranged from 103 to 158 hours. The elimination half-life is 3 to 4 hours and is independent of dose.

Glimepiride: Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about ⅓ of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1 is clinically meaningful is not clear.

When [^{14}C]glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80 to 90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent drug was recovered from urine or feces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.

Special Populations: No pharmacokinetic data are available for AVANDARYL in the following special populations. Information is provided for the individual components of AVANDARYL.

Gender: Rosiglitazone: Results of the population pharmacokinetics analysis showed that the mean oral clearance of rosiglitazone in female patients (n = 405) was approximately 6% lower compared to male patients of the same body weight (n = 642). Combination therapy with rosiglitazone and sulfonylureas improved glycemic control in both males and females with a greater therapeutic response observed in females. For a given body mass index (BMI), females tend to have a greater fat mass than males. Since the molecular target of rosiglitazone, PPARγ, is expressed in adipose tissues, this differentiating characteristic may account, at least in part, for

the greater response to rosiglitazone in combination with sulfonylureas in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.

Glimepiride: There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight.

Geriatric: Rosiglitazone: Results of the population pharmacokinetics analysis (n = 716 <65 years; n = 331 ≥65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone.

Glimepiride: Comparison of glimepiride pharmacokinetics in type 2 diabetes patients 65 years and younger with those older than 65 years was performed in a study using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the 2 age groups. The mean AUC at steady state for the older patients was about 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was about 11% higher than that for the younger patients. (See PRECAUTIONS, Geriatric Use.)

Hepatic Impairment: Therapy with AVANDARYL should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal) at baseline (see PRECAUTIONS, Hepatic Effects).

Rosiglitazone: Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound C_{max} and $AUC_{0\text{-}inf}$ were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects.

Glimepiride: No studies of glimepiride have been conducted in patients with hepatic insufficiency.

Race: Rosiglitazone: Results of a population pharmacokinetic analysis including subjects of white, black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of rosiglitazone.

Glimepiride: No pharmacokinetic studies to assess the effects of race have been performed, but in placebo-controlled studies of glimepiride in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n = 536), blacks (n = 63), and Hispanics (n = 63).

Renal Impairment: Rosiglitazone: There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients compared to subjects with normal renal function.

Glimepiride: A single-dose glimepiride, open-label study was conducted in 15 patients with renal impairment. Glimepiride (3 mg) was administered to 3 groups of patients with different levels of mean creatinine clearance (CL_{cr}); (Group I, CL_{cr} = 77.7 mL/min, n = 5), (Group II, CL_{cr} = 27.7 mL/min, n = 3), and (Group III, CL_{cr} = 9.4 mL/min, n = 7). Glimepiride was found to be well tolerated in all 3 groups. The results showed that glimepiride serum levels decreased as renal function decreased. However, M1 and M2 serum levels (mean AUC values)

increased 2.3 and 8.6 times from Group I to Group III. The apparent terminal half-life ($T_{½}$) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased (44.4%, 21.9%, and 9.3% for Groups I to III). A multiple-dose titration study was also conducted in 16 type 2 diabetes patients with renal impairment using doses ranging from 1 to 8 mg daily for 3 months. The results were consistent with those observed after single doses. All patients with a CL_{cr} less than 22 mL/min had adequate control of their glucose levels with a dosage regimen of only 1 mg daily. The results from this study suggest that a starting dose of 1 mg glimepiride, as contained in AVANDARYL 4 mg/1 mg, may be given to type 2 diabetes patients with kidney disease, and the dose may be titrated based on fasting glucose levels.

Pediatric: No pharmacokinetic data from studies in pediatric subjects are available for AVANDARYL.

Rosiglitazone: Pharmacokinetic parameters of rosiglitazone in pediatric patients were established using a population pharmacokinetic analysis with sparse data from 96 pediatric patients in a single pediatric clinical trial including 33 males and 63 females with ages ranging from 10 to 17 years (weights ranging from 35 to 178.3 kg). Population mean CL/F and V/F of rosiglitazone were 3.15 L/hr and 13.5 L, respectively. These estimates of CL/F and V/F were consistent with the typical parameter estimates from a prior adult population analysis.

Glimepiride: The pharmacokinetics of glimepiride (1 mg) were evaluated in a single-dose study conducted in 30 type 2 diabetic patients (male = 7; female = 23) between ages 10 and 17 years. The mean $AUC_{0\text{-last}}$ (338.8 ± 203.1 ng.hr/mL), C_{max} (102.4 ± 47.7 ng/mL), and $T_{½}$ (3.1 ± 1.7 hours) were comparable to those previously reported in adults ($AUC_{0\text{-last}}$ 315.2 ± 95.9 ng.hr/mL, C_{max} 103.2 ± 34.3 ng/mL, and $T_{½}$ 5.3 ± 4.1 hours).

Drug Interactions: Single oral doses of glimepiride in 14 healthy adult subjects had no clinically significant effect on the steady-state pharmacokinetics of rosiglitazone. No clinically significant reductions in glimepiride AUC and C_{max} were observed after repeat doses of rosiglitazone (8 mg once daily) for 8 days in healthy adult subjects.

Rosiglitazone: Drugs that Inhibit, Induce or are Metabolized by Cytochrome P450: In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. In vitro data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9. An inhibitor of CYP2C8 (such as gemfibrozil) may decrease the metabolism of rosiglitazone and an inducer of CYP2C8 (such as rifampin) may increase the metabolism of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response.

Rosiglitazone (4 mg twice daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinyl estradiol and norethindrone), which are predominantly metabolized by CYP3A4.

Gemfibrozil: Concomitant administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone

AUC by 127%, compared to the administration of rosiglitazone (4 mg once daily) alone. Given the potential for dose-related adverse events with rosiglitazone, a decrease in the dose of rosiglitazone may be needed when gemfibrozil is introduced (see PRECAUTIONS).

Rifampin: Rifampin administration (600 mg once a day), an inducer of CYP2C8, for 6 days is reported to decrease rosiglitazone AUC by 66%, compared to the administration of rosiglitazone (8 mg) alone (see PRECAUTIONS).[1]

Glyburide: Rosiglitazone (2 mg twice daily) taken concomitantly with glyburide (3.75 to 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy. Repeat doses of rosiglitazone (8 mg once daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and C_{max} of approximately 30%. In Japanese subjects, glyburide AUC and C_{max} slightly increased following coadministration of rosiglitazone.

Digoxin: Repeat oral dosing of rosiglitazone (8 mg once daily) for 14 days did not alter the steady-state pharmacokinetics of digoxin (0.375 mg once daily) in healthy volunteers.

Warfarin: Repeat dosing with rosiglitazone had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers.

Additional pharmacokinetic studies demonstrated no clinically relevant effect of acarbose, ranitidine, or metformin on the pharmacokinetics of rosiglitazone.

Glimepiride: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs) and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. When these drugs are administered to a patient receiving glimepiride, the patient should be observed closely for hypoglycemia. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid. When these drugs are administered to a patient receiving glimepiride, the patient should be closely observed for loss of control. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for hypoglycemia.

Drugs Metabolized by Cytochrome P450: A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is not known. There is a potential interaction of glimepiride with inhibitors (e.g. fluconazole) and inducers (e.g., rifampicin) of cytochrome P450 2C9.

Aspirin: Coadministration of aspirin (1 g three times daily) and glimepiride led to a 34% decrease in the mean glimepiride AUC and, therefore, a 34% increase in the mean CL/F. The mean C_{max} had a decrease of 4%. Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported.

H_2-Receptor Antagonists: Coadministration of either cimetidine (800 mg once daily) or ranitidine (150 mg twice daily) with a single 4-mg oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride, and no differences were seen in hypoglycemic symptomatology.

Beta-Blockers: Concomitant administration of propranolol (40 mg three times daily) and glimepiride significantly increased C_{max}, AUC, and $T_{½}$ of glimepiride by 23%, 22%, and 15%, respectively, and it decreased CL/F by 18%. The recovery of M1 and M2 from urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo. Pooled data from clinical trials in patients with type 2 diabetes showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of beta-blockers. However, if beta-blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

Warfarin: Concomitant administration of glimepiride tablets (4 mg once daily) did not alter the pharmacokinetic characteristics of R- and S-warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding. Glimepiride treatment did result in a slight, but statistically significant, decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride treatment were very small (3.3% and 9.9%, respectively) and are unlikely to be clinically important.

Ace Inhibitors: The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2 mg glimepiride were unaffected by coadministration of ramipril (an ACE inhibitor) 5 mg once daily in normal subjects. No hypoglycemic symptoms were reported.

Other: Although no specific interaction studies were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of aspirin and other salicylates, H_2-receptor antagonists, ACE inhibitors, calcium-channel blockers, estrogens, fibrates, NSAIDs, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone.

CLINICAL STUDIES

Drug-Naïve Patients with Type 2 Diabetes Mellitus: In a 28-week, randomized, double-blind clinical trial, 901 drug-naïve patients with type 2 diabetes inadequately controlled with diet and exercise alone (baseline mean fasting plasma glucose [FPG] 211 mg/dL and baseline mean HbA1c 9.1%) were started on AVANDARYL 4 mg/1 mg, rosiglitazone 4 mg, or glimepiride 1 mg. Doses could be increased at 4-week intervals to reach a target mean daily glucose of ≤110 mg/dL. Patients who received AVANDARYL were randomized to 1 of 2 titration schemes differing in the maximum total daily dose (4 mg/4 mg or 8 mg/4 mg). The maximum total daily dose was 8 mg for rosiglitazone monotherapy and 4 mg for glimepiride monotherapy. All treatments were administered as a once daily regimen. Improvements in FPG and HbA1c were

observed in patients treated with AVANDARYL compared to either rosiglitazone or glimepiride alone (see Table 2).

Table 2. Glycemic Parameters in a 28-Week Study of AVANDARYL in Drug-Naïve Patients with Type 2 Diabetes Mellitus

	Glimepiride	Rosiglitazone	AVANDARYL 4 mg/4 mg	AVANDARYL 8 mg/4 mg
Mean Final Dose	3.5 mg	7.5 mg	4.0 mg/3.2 mg	6.8 mg/2.9 mg
N	221	227	221	214
FPG (mg/dL) [mean (SD)]				
Baseline	211 (70)	212 (66)	207 (58)	214 (61)
Change from baseline	-42 (66)	-57 (58)	-70 (57)	-80 (57)
Treatment difference between				
– AVANDARYL and glimepiride	—	—	-30*	-37*
– AVANDARYL and rosiglitazone	—	—	-16*	-23*
% of patients with ≥30 mg/dL decrease from baseline	56%	64%	77%	85%
HbA1c (%) [mean (SD)]				
Baseline	9.0 (1.3)	9.1 (1.3)	9.0 (1.3)	9.2 (1.4)
Change from baseline	-1.7 (1.4)	-1.8 (1.5)	-2.4 (1.4)	-2.5 (1.4)
Treatment difference between				
– AVANDARYL and glimepiride	—	—	-0.6*	-0.7*
– AVANDARYL and rosiglitazone	—	—	-0.7*	-0.8*
% of patients with ≥0.7% decrease from baseline	82%	76%	93%	93%
% of patients at HbA1c Target <7.0%†	49%	46%	75%	72%

* Least squared means, $p<0.0001$ compared to monotherapy.

† Response is related to baseline HbA1c.

Treatment with AVANDARYL resulted in statistically significant improvements in FPG and HbA1c compared with each of the monotherapies. However, when considering choice of therapy for drug-naïve patients, the risk-benefit of initiating monotherapy or dual therapy should be

considered. In particular, the risk of hypoglycemia and weight gain with dual therapy should be taken into account. (See WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.)

The lipid profiles of rosiglitazone and glimepiride were consistent with the known profile of each monotherapy. AVANDARYL was associated with increases in HDL and LDL (3% to 4% for each) and decreases in triglycerides (-4%), that were not considered to be clinically meaningful.

Patients with Type 2 Diabetes Mellitus Previously Treated with Sulfonylureas: The safety and efficacy of rosiglitazone added to a sulfonylurea have been studied in clinical trials in patients with type 2 diabetes inadequately controlled on sulfonylureas alone. No clinical trials have been conducted with the fixed-dose combination of AVANDARYL in patients inadequately controlled on a sulfonylurea or who have initially responded to rosiglitazone alone and require additional glycemic control.

A total of 3,457 patients with type 2 diabetes participated in ten 24- to 26-week randomized, double-blind, placebo/active-controlled studies and one 2-year double-blind, active-controlled study in elderly patients designed to assess the efficacy and safety of rosiglitazone in combination with a sulfonylurea. Rosiglitazone 2 mg, 4 mg, or 8 mg daily, was administered either once daily (3 studies) or in divided doses twice daily (7 studies), to patients inadequately controlled on a submaximal or maximal dose of sulfonylurea.

In these studies, the combination of rosiglitazone 4 mg or 8 mg daily (administered as single or twice daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c compared to placebo plus sulfonylurea or further up-titration of the sulfonylurea. Table 3 shows pooled data for 8 studies in which rosiglitazone added to sulfonylurea was compared to placebo plus sulfonylurea.

Table 3. Glycemic Parameters in 24- to 26-Week Combination Studies of Rosiglitazone Plus Sulfonylurea

Twice Daily Divided Dosing (5 Studies)	**Sulfonylurea**	**Rosiglitazone 2 mg twice daily + sulfonylurea**	**Sulfonylurea**	**Rosiglitazone 4 mg twice daily + sulfonylurea**
N	397	497	248	346
FPG (mg/dL)				
Baseline (mean)	204	198	188	187
Change from baseline (mean)	11	-29	8	-43
Difference from sulfonylurea alone (adjusted mean)	-	-42*	-	-53*
% of patients with ≥30 mg/dL decrease from baseline	17%	49%	15%	61%
HbA1c (%)				
Baseline (mean)	9.4	9.5	9.3	9.6
Change from baseline (mean)	0.2	-1.0	0.0	-1.6
Difference from sulfonylurea alone (adjusted mean)	-	-1.1*	-	-1.4*
% of patients with ≥0.7% decrease from baseline	21%	60%	23%	75%
Once Daily Dosing (3 Studies)	**Sulfonylurea**	**Rosiglitazone 4 mg once daily + sulfonylurea**	**Sulfonylurea**	**Rosiglitazone 8 mg once daily + sulfonylurea**
N	172	172	173	176
FPG (mg/dL)				
Baseline (mean)	198	206	188	192
Change from baseline (mean)	17	-25	17	-43
Difference from sulfonylurea alone (adjusted mean)	-	-47*	-	-66*
% of patients with ≥30 mg/dL decrease from baseline	17%	48%	19%	55%
HbA1c (%)				
Baseline (mean)	8.6	8.8	8.9	8.9
Change from baseline	0.4	-0.5	0.1	-1.2

(mean)				
Difference from sulfonylurea alone (adjusted mean)	-	-0.9*	-	-1.4*
% of patients with ≥0.7% decrease from baseline	11%	36%	20%	68%

* p<0.0001 compared to sulfonylurea alone.

One of the 24- to 26-week studies included patients who were inadequately controlled on maximal doses of glyburide and switched to 4 mg of rosiglitazone daily as monotherapy; in this group, loss of glycemic control was demonstrated, as evidenced by increases in FPG and HbA1c.

In a 2-year double-blind study, elderly patients (aged 59 to 89 years) on half-maximal sulfonylurea (glipizide 10 mg twice daily) were randomized to the addition of rosiglitazone (n = 115, 4 mg once daily to 8 mg as needed) or to continued up-titration of glipizide (n = 110), to a maximum of 20 mg twice daily. Mean baseline FPG and HbA1c were 157 mg/dL and 7.72%, respectively, for the rosiglitazone plus glipizide arm and 159 mg/dL and 7.65%, respectively, for the glipizide up-titration arm. Loss of glycemic control (FPG ≥180 mg/dL) occurred in a significantly lower proportion of patients (2%) on rosiglitazone plus glipizide compared to patients in the glipizide up-titration arm (28.7%). About 78% of the patients on combination therapy completed the 2 years of therapy while only 51% completed on glipizide monotherapy. The effect of combination therapy on FPG and HbA1c was durable over the 2-year study period, with patients achieving a mean of 132 mg/dL for FPG and a mean of 6.98% for HbA1c compared to no change on the glipizide arm.

The pattern of LDL and HDL changes following therapy with rosiglitazone in combination with sulfonylureas was generally similar to those seen with rosiglitazone in monotherapy. Rosiglitazone as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids. The changes in triglycerides during therapy with rosiglitazone were variable and were generally not statistically different from placebo or glyburide controls.

INDICATIONS AND USAGE

AVANDARYL is indicated as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and glimepiride therapy is appropriate.

Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but also in maintaining the efficacy of drug therapy. Prior to initiation of therapy with AVANDARYL, secondary causes of poor glycemic control, e.g., infection, should be investigated and treated.

CONTRAINDICATIONS

AVANDARYL is contraindicated in patients with:

- Known hypersensitivity to rosiglitazone or glimepiride or any of the components of AVANDARYL.
- Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

WARNINGS

Glimepiride:

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes* 1970;19[Suppl. 2]:747-830). UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glimepiride-containing tablets and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

Rosiglitazone:

Cardiac Failure and Other Cardiac Effects: Rosiglitazone, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. In combination with insulin, thiazolidinediones may also increase the risk of other cardiovascular adverse events. Rosiglitazone should be discontinued if any deterioration in cardiac status occurs.

Patients with congestive heart failure (CHF) New York Heart Association (NYHA) Class 1 and 2 treated with rosiglitazone have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-controlled echocardiographic study was conducted in 224 patients with type 2 diabetes mellitus and NYHA Class 1 or 2 CHF (ejection fraction ≤45%) on background

antidiabetic and CHF therapy. An independent committee conducted a blinded evaluation of fluid-related events (including congestive heart failure) and cardiovascular hospitalizations according to predefined criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were reported by investigators. Although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed with rosiglitazone treatment compared to placebo during the 52-week study. (See Table 4.)

Table 4. Emergent Cardiovascular Adverse Events in Patients with Congestive Heart Failure (NYHA Class 1 and 2) treated with Rosiglitazone or Placebo (in Addition to Background Antidiabetic and CHF Therapy)

	Placebo	**Rosiglitazone**
Events	N = 114 n (%)	N = 110 n (%)
Adjudicated		
Cardiovascular Deaths	4 (4)	5 (5)
CHF Worsening – with overnight hospitalization – without overnight hospitalization	4 (4) 4 (4) 0 (0)	7 (6) 5 (5) 2 (2)
New or Worsening Edema	10 (9)	28 (25)
New or Worsening Dyspnea	19 (17)	29 (26)
Increases in CHF Medication	20 (18)	36 (33)
Cardiovascular Hospitalization*	15 (13)	21 (19)
Investigator-reported, Non-adjudicated		
Ischemic Adverse Events – Myocardial Infarction – Angina	5 (4) 2 (2) 3 (3)	10 (9) 5 (5) 6 (5)

* Includes hospitalization for any cardiovascular reason.

Patients with NYHA Class 3 and 4 cardiac status were not studied during the clinical trials. Rosiglitazone is not recommended in patients with NYHA Class 3 and 4 cardiac status.

In three 26-week trials in patients with type 2 diabetes, 216 received 4 mg of rosiglitazone plus insulin, 322 received 8 mg of rosiglitazone plus insulin, and 338 received insulin alone. These trials included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. In these clinical studies an increased incidence of edema, cardiac failure, and other cardiovascular adverse events was seen in patients on rosiglitazone and insulin combination therapy compared to insulin and placebo. Patients who

experienced cardiovascular events were on average older and had a longer duration of diabetes. These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of rosiglitazone. In this population, however, it was not possible to determine specific risk factors that could be used to identify all patients at risk of heart failure and other cardiovascular events on combination therapy. Three of 10 patients who developed cardiac failure on combination therapy during the double-blind part of the fixed-dose studies had no known prior evidence of congestive heart failure, or pre-existing cardiac condition.

In a double-blind study in type 2 diabetes patients with chronic renal failure (112 received 4 mg or 8 mg of rosiglitazone plus insulin and 108 received insulin control), there was no difference in cardiovascular adverse events with rosiglitazone in combination with insulin compared to insulin control.

Patients treated with combination rosiglitazone and insulin should be monitored for cardiovascular adverse events. This combination therapy should be discontinued in patients who do not respond as manifested by a reduction in HbA1c or insulin dose after 4 to 5 months of therapy or who develop any significant adverse events. (See ADVERSE REACTIONS.)

There are no studies that have evaluated the safety or effectiveness of AVANDARYL in combination with insulin. Therefore, the use of AVANDARYL in combination with insulin is not recommended.

PRECAUTIONS

General: Due to the mechanisms of action, rosiglitazone and glimepiride are active only in the presence of endogenous insulin. Therefore, AVANDARYL should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia: AVANDARYL is a combination tablet containing rosiglitazone and glimepiride, a sulfonylurea. All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Elderly patients are particularly susceptible to hypoglycemic action of glucose lowering drugs. Debilitated or malnourished patients, and those with adrenal, pituitary, renal, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. A starting dose of 1 mg glimepiride, as contained in AVANDARYL 4 mg/1 mg, followed by appropriate dose titration is recommended in these patients. (See CLINICAL PHARMACOLOGY, Special Populations, *Renal Impairment*.) Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Patients receiving rosiglitazone in combination with a sulfonylurea may be at risk for hypoglycemia, and a reduction in the dose of the sulfonylurea may be necessary (see DOSAGE AND ADMINISTRATION, Special Populations).

Loss of Control of Blood Glucose: When a patient stabilized on any antidiabetic 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 AVANDARYL and temporarily administer insulin. AVANDARYL may be reinstituted after the acute episode is resolved.

Edema: AVANDARYL should be used with caution in patients with edema. In a clinical study in healthy volunteers who received 8 mg of rosiglitazone once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo.

Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, AVANDARYL should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure (see WARNINGS, Rosiglitazone, Cardiac Failure and Other Cardiac Effects and PRECAUTIONS, Information for Patients).

In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with rosiglitazone, and may be dose related. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and rosiglitazone (see ADVERSE REACTIONS). The use of AVANDARYL in combination with insulin is not recommended (see WARNINGS, Rosiglitazone, Cardiac Failure and Other Cardiac Effects).

Macular Edema: Macular edema has been reported in postmarketing experience in some diabetic patients who were taking rosiglitazone or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. Patients with diabetes should have regular eye exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings. (See ADVERSE REACTIONS, Rosiglitazone.)

Weight Gain: Dose-related weight gain was seen with AVANDARYL, rosiglitazone alone, and rosiglitazone together with other hypoglycemic agents (see Table 5). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 5. Weight Changes (kg) From Baseline at Endpoint During Clinical Trials [Median (25^{th}, 75^{th}, Percentile)]

Monotherapy				
Duration	**Control Group**		**Rosiglitazone 4 mg**	**Rosiglitazone 8 mg**
26 weeks	Placebo	-0.9 (-2.8, 0.9) n = 210	1.0 (-0.9, 3.6) n = 436	3.1 (1.1, 5.8) n = 439
52 weeks	Sulfonylurea	2.0 (0, 4.0) n = 173	2.0 (-0.6, 4.0) n = 150	2.6 (0, 5.3) n = 157
Combination Therapy				
			Rosiglitazone plus Control Therapy	
Duration	**Control Group**		**Rosiglitazone 4 mg**	**Rosiglitazone 8 mg**
24-26 weeks	Sulfonylurea	0 (-1.0, 1.3) n = 1,155	2.2 (0.5, 4.0) n = 613	3.5 (1.4, 5.9) n = 841
26 weeks	Metformin	-1.4 (-3.2, 0.2) n = 175	0.8 (-1.0, 2.6) n = 100	2.1 (0, 4.3) n = 184
26 weeks	Insulin	0.9 (-0.5, 2.7) n = 162	4.1 (1.4, 6.3) n = 164	5.4 (3.4, 7.3) n = 150
AVANDARYL in Drug Naïve Patients				
Duration	**Control Groups**		**AVANDARYL 4 mg/4 mg**	**AVANDARYL 8 mg/4 mg**
28 weeks	Glimepiride	1.1 (-1.1, 3.2) n = 222	2.2 (0, 4.5) n = 221	2.9 (0, 5.8) n = 217
	Rosiglitazone	0.9 (-1.4, 3.2) n = 228		

In postmarketing experience with rosiglitazone alone or in combination with other hypoglycemic agents, there have been rare reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

Hematologic: Across all controlled clinical studies, decreases in hemoglobin and hematocrit (mean decreases in individual studies ≤1.0 gram/dL and ≤3.3%, respectively) were observed for rosiglitazone alone and in combination with other hypoglycemic agents. The changes occurred primarily during the first 3 months following initiation of therapy with rosiglitazone or following a dose increase in rosiglitazone. White blood cell counts also decreased slightly in patients treated with rosiglitazone. The observed changes may be related to the increased plasma volume observed with treatment with rosiglitazone and may be dose related.

Ovulation: Therapy with rosiglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking rosiglitazone (see PRECAUTIONS, Pregnancy, Pregnancy Category

C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known.

Although hormonal imbalance has been seen in preclinical studies (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility), the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with AVANDARYL should be reviewed.

Hepatic Effects: Another drug of the thiazolidinedione class, troglitazone, was associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death were reported during clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations in liver enzymes (ALT >3X upper limit of normal) compared to placebo. Very rare cases of reversible jaundice were also reported.

In pre-approval clinical studies in 4,598 patients treated with rosiglitazone, encompassing approximately 3,600 patient years of exposure, there was no signal of drug-induced hepatotoxicity or elevation of ALT levels. In the pre-approval controlled trials, 0.2% of patients treated with rosiglitazone had elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with rosiglitazone were reversible and were not clearly causally related to therapy with rosiglitazone.

In postmarketing experience with rosiglitazone, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established. Rosiglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death during clinical use. Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with AVANDARYL undergo periodic monitoring of liver enzymes.

With sulfonylureas, including glimepiride, there may be an elevation of liver enzyme levels in rare cases. In isolated instances, impairment of liver function (e.g., with cholestasis and jaundice), as well as hepatitis (which may also lead to liver failure) have been reported.

Liver enzymes should be checked prior to the initiation of therapy with AVANDARYL in all patients and periodically thereafter per the clinical judgement of the healthcare professional. Therapy with AVANDARYL should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with AVANDARYL should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with AVANDARYL in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time

ALT levels increase to >3X the upper limit of normal in patients on therapy with AVANDARYL, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with AVANDARYL should be discontinued.

If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with AVANDARYL should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

There are no data available from clinical trials to evaluate the safety of AVANDARYL in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. AVANDARYL should not be used in patients who experienced jaundice while taking troglitazone.

Laboratory Tests: Periodic fasting glucose and HbA1c measurements should be performed to monitor therapeutic response.

Liver enzyme monitoring is recommended prior to initiation of therapy with AVANDARYL in all patients and periodically thereafter (see PRECAUTIONS, Hepatic Effects).

Information for Patients: Patients should be informed of the potential risks and advantages of AVANDARYL and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, weight loss, and a regular exercise program because these methods help improve insulin sensitivity. The importance of regular testing of blood glucose and glycosylated hemoglobin (HbA1c) should be emphasized. Patients should be advised that the sulfonylurea effect of AVANDARYL can begin to take effect within days after initiation, however it can take 2 to 3 months to see the full effect of glycemic improvement.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Patients should be informed that blood will be drawn to check their liver function prior to the start of therapy and periodically thereafter per the clinical judgement of the healthcare professional. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician. Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on AVANDARYL should immediately report these symptoms to their physician.

AVANDARYL should be taken with the first meal of the day.

Therapy with rosiglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDARYL (see PRECAUTIONS, Pregnancy, Pregnancy Category C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known.

Drug Interactions: ***Rosiglitazone: Drugs Metabolized by Cytochrome P450:*** An inhibitor of CYP2C8 (such as gemfibrozil) may increase the AUC of rosiglitazone and an inducer of CYP2C8 (such as rifampin) may decrease the AUC of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response. (See CLINICAL PHARMACOLOGY, Drug Interactions, *Rosiglitazone*.)

Glimepiride: Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid. When these drugs are administered to a patient receiving glimepiride, the patient should be closely observed for loss of control. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for hypoglycemia.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is not known. Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 2C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid. (See CLINICAL PHARMACOLOGY, Drug Interactions, *Glimepiride*.)

Carcinogenesis, Mutagenesis, Impairment of Fertility: No animal studies have been conducted with AVANDARYL. The following data are based on findings in studies performed with rosiglitazone or glimepiride alone.

Rosiglitazone: Carcinogenesis: A 2-year carcinogenicity study was conducted in Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately 12 times human AUC at the maximum recommended human daily dose). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05 mg/kg/day, 0.3 mg/kg/day, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times human AUC at the maximum recommended human daily dose for male and female rats, respectively).

Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses ≥1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses ≥0.3 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic activation.

Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose). In juvenile rats dosed from 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in females (approximately 68 times human AUC at the maximum recommended daily dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

Glimepiride: Carcinogenesis: Studies in rats at doses of up to 5,000 parts per million (ppm) in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation which was dose related and is thought to be the result of chronic pancreatic stimulation. The no-effect dose for adenoma formation in mice in this study was 320 ppm in complete feed, or 46 to 54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose based on surface area.

Mutagenesis: Glimepiride was non-mutagenic in a battery of in vitro and in vivo mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, mouse micronucleus test).

Impairment of Fertility: There was no effect of glimepiride on male mouse fertility in animals exposed up to 2,500 mg/kg body weight (>1,700 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4,000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

Animal Toxicology: *Rosiglitazone:* Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose, respectively). Effects in juvenile rats were consistent with those seen in adults. Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

Glimepiride: Reduced serum glucose values and degranulation of the pancreatic beta cells were observed in beagle dogs exposed to glimepiride 320 mg/kg/day for 12 months (approximately 1,000 times the recommended human dose based on surface area). No evidence

of tumor formation was observed in any organ. One female and one male dog developed bilateral subcapsular cataracts. Non-GLP studies indicated that glimepiride was unlikely to exacerbate cataract formation. Evaluation of the co-cataractogenic potential of glimepiride in several diabetic and cataract rat models was negative and there was no adverse effect of glimepiride on bovine ocular lens metabolism in organ culture (see ADVERSE EVENTS, *Human Ophthalmology Data*).

Pregnancy: Pregnancy Category C. 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 monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible. AVANDARYL should not be used during pregnancy.

There are no adequate and well-controlled studies with AVANDARYL or its individual components in pregnant women. No animal studies have been conducted with AVANDARYL. The following data are based on findings in studies performed with rosiglitazone or glimepiride individually.

Rosiglitazone: There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced the number of uterine implantations and live offspring when juvenile female rats were treated at 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day (approximately 4 times human AUC at the maximum recommended daily dose). There was no effect on pre- or post-natal survival or growth.

Glimepiride: Glimepiride did not produce teratogenic effects in rats exposed orally up to 4,000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area). Glimepiride has been shown to be associated with intrauterine fetal death in rats when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

In some studies in rats, offspring of dams exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. Significant concentrations of glimepiride were observed in the serum and breast milk of the dams as well as in the serum of the pups. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride. Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives.

Labor and Delivery: The effect of AVANDARYL or its components on labor and delivery in humans is unknown.

Nursing Mothers: No studies have been conducted with AVANDARYL. It is not known whether rosiglitazone and/or glimepiride is excreted in human milk. Because many drugs are excreted in human milk, AVANDARYL should not be administered to a nursing woman. If AVANDARYL is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered (see PRECAUTIONS, Pregnancy, Pregnancy Category C).

Rosiglitazone: Drug-related material was detected in milk from lactating rats.

Glimepiride: In rat reproduction studies, significant concentrations of glimepiride were observed in the serum and breast milk of the dams, as well as in the serum of the pups. Although it is not known whether glimepiride is excreted in human milk, other sulfonylureas are excreted in human milk.

Pediatric Use: Safety and effectiveness of AVANDARYL in pediatric patients have not been established. AVANDARYL and its components, rosiglitazone and glimepiride, are not indicated for use in pediatric patients.

Geriatric Use: *Rosiglitazone:* Results of the population pharmacokinetic analysis showed that age does not significantly affect the pharmacokinetics of rosiglitazone (see CLINICAL PHARMACOLOGY, Special Populations, *Geriatric*). Therefore, no dosage adjustments are required for the elderly. In controlled clinical trials, no overall differences in safety and effectiveness between older (≥65 years) and younger (<65 years) patients were observed.

Glimepiride: In US clinical studies of glimepiride, 608 of 1,986 patients were 65 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Comparison of glimepiride pharmacokinetics in type 2 diabetes patients ≤65 years (n = 49) and those >65 years (n = 42) was performed in a study using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the 2 age groups (see CLINICAL PHARMACOLOGY, Special Populations, *Geriatric*).

The drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs. In elderly, debilitated, or malnourished patients, or in patients with renal, hepatic or adrenal insufficiency, the starting dose, dose increments, and maintenance dosage should be conservative based upon blood glucose levels prior to and after initiation of treatment to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents (see CLINICAL PHARMACOLOGY, Special Populations, *Renal Impairment*; PRECAUTIONS, General; and DOSING AND ADMINISTRATION, Special Populations).

ADVERSE REACTIONS

Adverse events occurring at a frequency of ≥5% in any treatment group in the 28-week double-blind trial of AVANDARYL in drug-naïve patients with type 2 diabetes mellitus are presented in Table 9. Patients in this trial were started on AVANDARYL 4 mg/1 mg, rosiglitazone 4 mg, or glimepiride 1 mg. Doses could be increased at 4-week intervals to reach a maximum total daily dose of either 4 mg/4 mg or 8 mg/4 mg for AVANDARYL, 8 mg for rosiglitazone monotherapy or 4 mg for glimepiride monotherapy.

Table 9. Adverse Events (≥5% in Any Treatment Group) Reported by Drug-Naïve Patients in a 28-Week Double-Blind Clinical Trial of AVANDARYL

Preferred term	Glimepiride Monotherapy	Rosiglitazone Monotherapy	AVANDARYL 4 mg/4 mg	AVANDARYL 8 mg/4 mg
	N = 222	N = 230	N = 224	N = 218
	%	%	%	%
Headache	2.3	6.1	3.1	6.0
Nasopharyngitis	3.6	5.2	4.0	4.6
Hypertension	3.6	5.2	3.1	2.3
Hypoglycemia*	4.1	0.4	3.6	5.5

* As documented by symptoms and a fingerstick blood glucose measurement of <50 mg/dL.

Hypoglycemia was reported to be generally mild to moderate in intensity and none of the reported events of hypoglycemia resulted in withdrawal from the study. Hypoglycemia requiring parenteral treatment (i.e., intravenous glucose or glucagon injection) was observed in 3 (0.7%) patients treated with AVANDARYL.

Edema was reported by 3.2% of patients on AVANDARYL, 3.0% on rosiglitazone alone, and 2.3% on glimepiride alone.

Congestive heart failure was observed in 1 (0.2%) patient treated with AVANDARYL and in 1 (0.4%) patient treated with rosiglitazone monotherapy.

Studies utilizing rosiglitazone in combination with a sulfonylurea provide support for the use of AVANDARYL. Adverse event data from these trials, in addition to adverse events reported with the use of rosiglitazone and glimepiride as monotherapy, are presented below.

Rosiglitazone: The most common adverse experiences with rosiglitazone monotherapy (≥5%) were upper respiratory tract infection, injury, and headache. Overall, the types of adverse experiences reported when rosiglitazone was added to a sulfonylurea were similar to those during monotherapy with rosiglitazone. In controlled combination therapy studies with sulfonylureas, mild to moderate hypoglycemic symptoms, which appear to be dose related, were reported. Few patients were withdrawn for hypoglycemia (<1%) and few episodes of hypoglycemia were considered to be severe (<1%).

Events of anemia and edema tended to be reported more frequently at higher doses, and were generally mild to moderate in severity and usually did not require discontinuation of treatment with rosiglitazone.

Edema was reported by 4.8% of patients receiving rosiglitazone compared to 1.3% on placebo, and 1.0% on sulfonylurea monotherapy. The reporting rate of edema was higher for rosiglitazone 8 mg added to a sulfonylurea (12.4%) compared to other combinations, with the exception of insulin. Anemia was reported by 1.9% of patients receiving rosiglitazone compared to 0.7% on placebo, 0.6% on sulfonylurea monotherapy, and 2.3% on rosiglitazone in combination with a sulfonylurea. Overall, the types of adverse experiences reported when rosiglitazone was added to a sulfonylurea were similar to those during monotherapy with rosiglitazone.

In 26-week double-blind, fixed-dose studies, edema was reported with higher frequency in the rosiglitazone plus insulin combination trials (insulin, 5.4%; and rosiglitazone in combination with insulin, 14.7%). Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with rosiglitazone.

In postmarketing experience in patients receiving thiazolidinedione therapy, serious adverse events potentially related to volume expansion (e.g., congestive heart failure, pulmonary edema with or without a fatal outcomes, and pleural effusions) have been reported. (See WARNINGS, Rosiglitazone, Cardiac Failure and Other Cardiac Effects.)

In postmarketing experience with rosiglitazone, angioedema and urticaria have been reported rarely.

Postmarketing reports of new onset or worsening diabetic macular edema with decreased visual acuity have also been received (see PRECAUTIONS, Macular Edema).

Glimepiride: Hypoglycemia: The incidence of hypoglycemia with glimepiride, as documented by blood glucose values <60 mg/dL, ranged from 0.9% to 1.7% in 2 large, well-controlled, 1-year studies. In patients treated with glimepiride in US placebo-controlled trials (n = 746), adverse events, other than hypoglycemia, considered to be possibly or probably related to study drug that occurred in more than 1% of patients included dizziness (1.7%), asthenia (1.6%), headache (1.5%), and nausea (1.1%).

Gastrointestinal Reactions: Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was less than 1%. In rare cases, there may be an elevation of liver enzyme levels. In isolated instances, impairment of liver function (e.g.,

with cholestasis and jaundice), as well as hepatitis, which may also lead to liver failure have been reported with sulfonylureas, including glimepiride.

Dermatologic Reactions: Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of glimepiride. If those hypersensitivity reactions persist or worsen, the drug should be discontinued. Porphyria cutanea tarda, photosensitivity reactions, and allergic vasculitis have been reported with sulfonylureas, including glimepiride.

Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas, including glimepiride.

Metabolic Reactions: Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas, including glimepiride. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, including glimepiride, and it has been suggested that certain sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Other Reactions: Changes in accommodation and/or blurred vision may occur with the use of glimepiride. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment. In placebo-controlled trials of glimepiride, the incidence of blurred vision was placebo, 0.7%, and glimepiride, 0.4%.

Human Ophthalmology Data: Ophthalmic examinations were carried out in more than 500 subjects during long-term studies of glimepiride using the methodology of Taylor and West and Laties et al. No significant differences were seen between glimepiride and glyburide in the number of subjects with clinically important changes in visual acuity, intraocular tension, or in any of the 5 lens-related variables examined. Ophthalmic examinations were carried out during long-term studies using the method of Chylack et al. No significant or clinically meaningful differences were seen between glimepiride and glipizide with respect to cataract progression by subjective LOCS II grading and objective image analysis systems, visual acuity, intraocular pressure, and general ophthalmic examination (see PRECAUTIONS, Animal Toxicology, *Glimepiride*).

Pediatric Use: Safety and effectiveness of AVANDARYL in pediatric patients have not been established. AVANDARYL and its individual components, rosiglitazone and glimepiride, are not indicated for use in pediatric patients.

OVERDOSAGE

Rosiglitazone: Limited data are available with regard to overdosage in humans. In clinical studies in volunteers, rosiglitazone has been administered at single oral doses of up to 20 mg and was well tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

Glimepiride: Overdosage of sulfonylureas, including glimepiride, can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. 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 IV injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

- AVANDARYL is available for oral administration as tablets containing a fixed dose of 4 mg rosiglitazone with variable doses of glimepiride (1 mg, 2 mg, or 4 mg) in a single tablet formulation.
- AVANDARYL should be given once daily with the first meal of the day. If a dose is forgotten, the following dose must not be doubled.
- Therapy with AVANDARYL should be individualized for each patient. The risk-benefit of initiating monotherapy versus dual therapy with AVANDARYL should be considered. (See CLINICAL TRIALS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.)

Starting Dose:

- The recommended starting dose is 4 mg/1 mg administered once daily with the first meal of the day. For patients already treated with a sulfonylurea or a thiazolidinedione, a starting dose of 4 mg/2 mg may be considered.
- When switching from combination therapy of rosiglitazone plus glimepiride as separate tablets, the usual starting dose of AVANDARYL is the dose of rosiglitazone and glimepiride already being taken.

Dose Titration:

- Dose increases should be individualized according to the glycemic response of the patient.
- Patients who may be more sensitive to glimepiride (see PRECAUTIONS, Hypoglycemia), including the elderly, debilitated, or malnourished, and those with renal, hepatic, or adrenal insufficiency, should be carefully titrated to avoid hypoglycemia.
- If hypoglycemia occurs during up-titration of the dose or while maintained on therapy, a dosage reduction of the glimepiride component of AVANDARYL may be considered.

- For **patients previously treated with thiazolidinedione monotherapy** and switched to AVANDARYL, dose titration of the glimepiride component of AVANDARYL is recommended if patients are not adequately controlled after 1 to 2 weeks.
- **Increases in glimepiride component:** The glimepiride component may be increased in no more than 2 mg increments. After an increase in the dosage of the glimepiride component, dose titration of AVANDARYL is recommended if patients are not adequately controlled after 1 to 2 weeks.
- For **patients previously treated with sulfonylurea monotherapy** and switched to AVANDARYL, it may take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of the rosiglitazone component. Therefore, dose titration of the rosiglitazone component of AVANDARYL is recommended if patients are not adequately controlled after 8 to 12 weeks. Patients should be observed carefully (1 to 2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to AVANDARYL due to potential overlapping of drug effect.
- **Increases in rosiglitazone component:** After an increase in the dosage of the rosiglitazone component, dose titration of AVANDARYL is recommended if patients are not adequately controlled after 2 to 3 months. Further increases in the dose of rosiglitazone should be accompanied by careful monitoring for adverse events related to fluid retention. (See WARNINGS, Rosiglitazone, Cardiac Failure and Other Cardiac Events.)

Maximum Dose:

- The maximum recommended daily dose is 8 mg rosiglitazone/4 mg glimepiride (given as two AVANDARYL 4 mg/2 mg tablets given before the first meal of the day).

No studies have been performed specifically examining the safety and efficacy of AVANDARYL in patients previously treated with other oral hypoglycemic agents and switched to AVANDARYL. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur. (See INDICATIONS AND USAGE.)

Specific Patient Populations:

- ***Pregnancy and Lactation:*** AVANDARYL should not be used during pregnancy or in nursing mothers.
- ***Pediatric Use:*** Safety and effectiveness of AVANDARYL in pediatric patients have not been established. AVANDARYL and its components, rosiglitazone and glimepiride, are not indicated for use in pediatric patients.
- ***Elderly and Malnourished Patients and those with Renal, Hepatic, or Adrenal Insufficiency:*** In elderly, debilitated, or malnourished patients, or in patients with renal, hepatic, or adrenal insufficiency, the starting dose, dose increments, and maintenance dosage of AVANDARYL should be conservative to avoid hypoglycemic reactions. (See CLINICAL PHARMACOLOGY, Special Populations, and PRECAUTIONS, Hypoglycemia.)
- ***Hepatic Impairment:*** Therapy with AVANDARYL should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT

>2.5X upper limit of normal at start of therapy) (see PRECAUTIONS, Hepatic Effects and CLINICAL PHARMACOLOGY, Special Populations, *Hepatic Impairment*). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with AVANDARYL and periodically thereafter (see PRECAUTIONS, Hepatic Effects).

HOW SUPPLIED

Tablets: Each tablet contains rosiglitazone as the maleate and glimepiride as follows:

4 mg/1 mg – yellow, rounded triangular tablet, gsk debossed on one side and 4/1 on the other.
4 mg/2 mg – orange, rounded triangular tablet, gsk debossed on one side and 4/2 on the other.
4 mg/4 mg – pink, rounded triangular tablet, gsk debossed on one side and 4/4 on the other.

4 mg/1 mg bottles of 30: NDC 0007-3151-13
4 mg/2 mg bottles of 30: NDC 0007-3152-13
4 mg/4 mg bottles of 30: NDC 0007-3153-13

STORAGE

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container.

REFERENCES

1. Park JY, Kim KA, Kang MH, et al. Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects. *Clin Pharmacol Ther* 2004;75:157-162.

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PATIENT INFORMATION

AVANDARYL™ (ah-VAN-duh-ril)

Rosiglitazone Maleate and Glimepiride Tablets

Read the Patient Information that comes with AVANDARYL before you start taking the medication and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about AVANDARYL, ask your doctor or pharmacist.

What is AVANDARYL?

AVANDARYL is a prescription medicine that contains 2 medicines to treat diabetes, rosiglitazone maleate (AVANDIA) and glimepiride (AMARYL). AVANDARYL is used with diet and exercise to treat type 2 ("adult-onset" or "non-insulin dependent") diabetes mellitus ("high blood sugar").

Glimepiride can help your body release more of its own insulin. Rosiglitazone can help your body respond better to the insulin made in your body. These medicines can work together to help control your blood sugar.

Diet, weight loss, and exercise can help your body use its blood sugar better. In order for AVANDARYL to work best, it is very important to exercise, lose excess weight, and follow the diet recommended for your diabetes.

What is Type 2 Diabetes?

Type 2 diabetes happens when a person does not make enough insulin or does not respond normally to the insulin their body makes. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, heart disease, loss of limbs, and blindness. The main goal of treating diabetes is to lower your blood sugar to a normal level. Lowering and controlling blood sugar may help prevent or delay complications of diabetes such as heart disease, kidney disease, or blindness. High blood sugar can be lowered by diet and exercise, by certain medicines taken by mouth, and by insulin shots.

Who should not take AVANDARYL?

Do not take AVANDARYL if you:

- are allergic to any of the ingredients in AVANDARYL. The active ingredients in AVANDARYL are rosiglitazone maleate and glimepiride. See the end of this leaflet for a list of all ingredients in AVANDARYL.
- have had diabetic ketoacidosis. This condition should be treated with insulin.

AVANDARYL has not been studied in children under 18 years of age and is not recommended for use in children under 18 years of age.

What should I tell my doctor before starting AVANDARYL?

You and your doctor will decide what treatment is best for you. Tell your doctor about all your medical conditions, including if you:

- **have heart problems or heart failure.** AVANDARYL can cause your body to keep extra fluid (fluid retention) which leads to swelling and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure.
- **have type 1 ("juvenile") diabetes.** You should not take AVANDARYL if you have type 1 diabetes.
- **have liver problems.** Your doctor should do blood tests to check your liver before you start taking AVANDARYL and during treatment as needed.
- **had liver problems while taking REZULIN® (troglitazone), another medicine for diabetes.**
- **have kidney problems.** If patients with kidney problems use AVANDARYL, they may need a lower dose of the medication.
- **are pregnant or trying to become pregnant.** It is not known if AVANDARYL can harm your unborn baby. You and your doctor should talk about the best way to control your high blood sugar during pregnancy. You should not use AVANDARYL if you are pregnant or trying to get pregnant.
- **are a premenopausal woman (before the "change of life") who does not have regular monthly periods.** AVANDARYL may increase your chances of becoming pregnant. Talk to your doctor about birth control choices while taking AVANDARYL.
- **are breastfeeding.** It is not known if AVANDARYL passes into breast milk. You should not use AVANDARYL while breastfeeding.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. AVANDARYL and certain other medicines can affect each other and lead to serious side effects including high blood sugar or low blood sugar. Keep a list of all the medicines you take. Show this list to your doctor and pharmacist before you start a new medicine. They will tell you if it is okay to take AVANDARYL with other medicines.

How should I take AVANDARYL?

- Take AVANDARYL by mouth once a day with your first main meal. Your doctor may need to adjust your dose until your blood sugar is better controlled.
- It usually takes a few days for AVANDARYL to start lowering your blood sugar. It may take 2 to 3 months to see the full effect on your blood sugar level.
- If you miss a dose of AVANDARYL, take your pill as soon as you remember unless it is time to take your next dose. Take your next dose at the usual time. Do not take a double dose to make up for a missed dose.
- If you take too much AVANDARYL, call your doctor or poison control center right away. Too much AVANDARYL can make your blood sugar level too low.

- Test your blood sugar regularly as your doctor tells you.
- Diet and exercise can help your body use its blood sugar better. It is important to stay on your recommended diet, lose excess weight, and get regular exercise while taking AVANDARYL.
- Your doctor should do blood tests to check your liver before you start AVANDARYL and during treatment as needed. Your doctor should also do regular blood testing [for example, blood glucose ("sugar") or glycosylated HbA1c ("A1c" or HbA1c)] to monitor your response to AVANDARYL.
- Call your doctor if you get sick, injured, or have surgery. AVANDARYL may not control your blood sugar levels during these times. Your doctor may need to stop AVANDARYL for a short time and give you insulin to control your blood sugar level.

What are possible serious side effects of AVANDARYL?

Talk to your doctor about these side effects:

- **heart failure.** AVANDARYL can cause your body to keep extra fluid (fluid retention), which leads to swelling and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. See "**swelling (edema) from fluid retention**" section below.
- **low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness or hunger may mean that your blood sugar is too low. This can happen if you skip meals, drink alcohol, use another medicine that lowers blood sugar, exercise (particularly hard or long), or if you have certain medical problems. Call your doctor if you have low blood sugar.
- **high blood sugar or loss of control of blood sugar (hyperglycemia).** If you have fever, an infection, trauma, or surgery, your doctor may temporarily stop the AVANDARYL and treat the high blood sugar with insulin.
- **swelling (edema) from fluid retention.** See "**heart failure**" section above. Call your doctor right away if you have symptoms such as:
  -swelling or fluid retention, especially in the ankles or legs
  -shortness of breath or trouble breathing, especially when you lie down
  -an unusually fast increase in weight
  -unusual tiredness
- **weight gain.** AVANDARYL can cause weight gain that may be due to fluid retention or extra body fat. Weight gain can be a serious problem for people with certain conditions including heart problems. Call your doctor if you have an unusually fast increase in weight.
- **low red blood cell count (anemia).**
- **ovulation (release of egg from an ovary in women) leading to pregnancy.** Ovulation may happen in premenopausal women who do not have regular monthly periods. This can increase the chance of pregnancy.
- **liver problems.** It is important for your liver to be working normally when you take AVANDARYL. Your doctor should do blood tests to check your liver before you start taking AVANDARYL and during treatment as needed.

Call your doctor right away if you have unexplained symptoms such as:

-nausea or vomiting
-stomach pain
-unusual or unexplained tiredness
-loss of appetite
-dark urine
-yellowing of your skin or the whites of your eyes

The most common side effects with AVANDARYL include cold-like symptoms, injury, and dizziness.

How should I store AVANDARYL?

- Store AVANDARYL at room temperature, 59° to 86° F (15° to 30° C). Keep AVANDARYL in the container it comes in.
- Safely throw away AVANDARYL that is out of date or no longer needed.
- Keep AVANDARYL and all medicines out of the reach of children.

General information about AVANDARYL

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use AVANDARYL for a condition for which it was not prescribed. Do not give AVANDARYL to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about AVANDARYL. If you would like more information , talk with your doctor. You can ask your doctor or pharmacist for information about AVANDARYL that is written for healthcare professionals. You can also find out more about AVANDARYL by calling 1-888-825-5249 or visiting the website www.AVANDARYL.com.

What are the ingredients in AVANDARYL?

Active Ingredients: rosiglitazone maleate and glimepiride.

Inactive Ingredients: Hypromellose 2910, lactose monohydrate, macrogol (polyethylene glycol) magnesium stearate, microcrystalline cellulose, sodium starch glycolate, titanium dioxide, triacetin, and 1 or more of the following: Yellow, red, or black iron oxides.

Always check to make sure that the medicine you are taking is the correct one. The dosage strength and appearance of each tablet of AVANDARYL (rosiglitazone maleate and glimepiride) are as follows:

4 mg/1 mg – yellow, rounded triangular tablet, “gsk” on one side and “4/1” on the other.

4 mg/2 mg – orange, rounded triangular tablet, “gsk” on one side and “4/2” on the other.

4 mg/4 mg – pink, rounded triangular tablet, “gsk” on one side and “4/4” on the other.

AVANDARYL is a trademark and AVANDIA is a registered trademark of GlaxoSmithKline.

AMARYL is a registered trademark of AVENTIS Pharmaceuticals Inc.

REZULIN is a registered trademark of Parke-Davis Pharmaceuticals Ltd.

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