

PRESCRIBING INFORMATION

AVANDARYL™

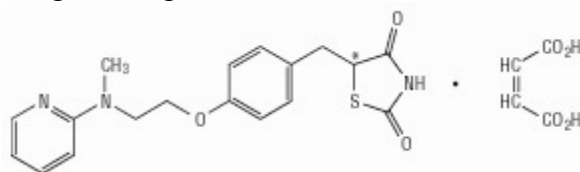
(rosiglitazone maleate and glimepiride)

Tablets

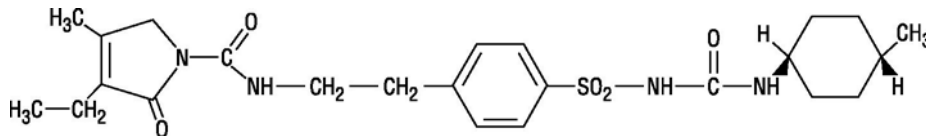
DESCRIPTION

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 (\pm)-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 $C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$. 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.

35 **CLINICAL PHARMACOLOGY**

36 **Mechanism of Action:** AVANDARYL combines 2 antidiabetic agents with complementary
37 mechanisms of action to improve glycemic control in patients with type 2 diabetes:

38 Rosiglitazone maleate, a member of the thiazolidinedione class, and glimepiride, a member of
39 the sulfonylurea class. Thiazolidinediones are insulin-sensitizing agents that act primarily by
40 enhancing peripheral glucose utilization, whereas sulfonylureas act primarily by stimulating
41 release of insulin from functioning pancreatic beta cells.

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

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

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

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

69 **Pharmacokinetics:** In a bioequivalence study of AVANDARYL 4 mg/4 mg, the area under
70 the curve (AUC) and maximum concentration (C_{max}) of rosiglitazone following a single dose of
71 the combination tablet were bioequivalent to rosiglitazone 4 mg concomitantly administered with
72 glimepiride 4 mg under fasted conditions. The AUC of glimepiride following a single fasted
73 4 mg/4 mg dose was equivalent to glimepiride concomitantly administered with rosiglitazone,
74 while the C_{max} was 13% lower when administered as the combination tablet (see Table 1).

75
76

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

Parameter (Units)	Rosiglitazone		Glimepiride	
	Regimen A	Regimen B	Regimen A	Regimen B
AUC _{0-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-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 _{1/2} (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)

77 AUC = area under the curve; C_{max} = maximum concentration; T_{1/2} = terminal half-life;
78 T_{max} = time of maximum concentration.
79 Regimen A = AVANDARYL 4 mg/4 mg tablet; Regimen B = Concomitant dosing of a
80 rosiglitazone 4 mg tablet AND a glimepiride 4 mg tablet.
81 Data presented as geometric mean (range), except T_{1/2} which is presented as arithmetic mean
82 (range) and T_{max}, which is presented as median (range).
83

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

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

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

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

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

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

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

118 **Glimepiride:** Glimepiride is completely metabolized by oxidative biotransformation after
119 either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative
120 (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 has been shown to be involved in
121 the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several
122 cytosolic enzymes. M1, but not M2, possesses about $\frac{1}{3}$ of the pharmacological activity as
123 compared to its parent in an animal model; however, whether the glucose-lowering effect of M1
124 is clinically meaningful is not clear.

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

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

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

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

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

145 **Geriatric: Rosiglitazone:** Results of the population pharmacokinetics analysis (n = 716
146 <65 years; n = 331 ≥65 years) showed that age does not significantly affect the pharmacokinetics
147 of rosiglitazone.

148 **Glimepiride:** Comparison of glimepiride pharmacokinetics in type 2 diabetes patients
149 65 years and younger with those older than 65 years was performed in a study using a dosing
150 regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics
151 between the 2 age groups. The mean AUC at steady state for the older patients was about 13%
152 lower than that for the younger patients; the mean weight-adjusted clearance for the older
153 patients was about 11% higher than that for the younger patients. (See PRECAUTIONS,
154 Geriatric Use.)

155 **Hepatic Impairment:** Therapy with AVANDARYL should not be initiated if the patient
156 exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT
157 >2.5X upper limit of normal) at baseline (see PRECAUTIONS, Hepatic Effects).

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

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

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

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

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

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

181 increased 2.3 and 8.6 times from Group I to Group III. The apparent terminal half-life ($T_{1/2}$) for
182 glimepiride did not change, while the half-lives for M1 and M2 increased as renal function
183 decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased
184 (44.4%, 21.9%, and 9.3% for Groups I to III). A multiple-dose titration study was also conducted
185 in 16 type 2 diabetes patients with renal impairment using doses ranging from 1 to 8 mg daily for
186 3 months. The results were consistent with those observed after single doses. All patients with a
187 CL_{cr} less than 22 mL/min had adequate control of their glucose levels with a dosage regimen of
188 only 1 mg daily. The results from this study suggest that a starting dose of 1 mg glimepiride, as
189 contained in AVANDARYL 4 mg/1 mg, may be given to type 2 diabetes patients with kidney
190 disease, and the dose may be titrated based on fasting glucose levels.

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

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

199 **Glimepiride:** The pharmacokinetics of glimepiride (1 mg) were evaluated in a single-dose
200 study conducted in 30 type 2 diabetic patients (male = 7; female = 23) between ages 10 and
201 17 years. The mean AUC_{0-last} (338.8 ± 203.1 ng.hr/mL), C_{max} (102.4 ± 47.7 ng/mL), and $T_{1/2}$
202 (3.1 ± 1.7 hours) were comparable to those previously reported in adults (AUC_{0-last}
203 315.2 ± 95.9 ng.hr/mL, C_{max} 103.2 ± 34.3 ng/mL, and $T_{1/2}$ 5.3 ± 4.1 hours).

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

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

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

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

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

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

227 **Glyburide:** Rosiglitazone (2 mg twice daily) taken concomitantly with glyburide (3.75 to
228 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations
229 in diabetic patients stabilized on glyburide therapy. Repeat doses of rosiglitazone (8 mg once
230 daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and
231 C_{max} of approximately 30%. In Japanese subjects, glyburide AUC and C_{max} slightly increased
232 following coadministration of rosiglitazone.

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

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

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

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

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

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

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

261 **H₂-Receptor Antagonists:** Coadministration of either cimetidine (800 mg once daily)
262 or ranitidine (150 mg twice daily) with a single 4-mg oral dose of glimepiride did not
263 significantly alter the absorption and disposition of glimepiride, and no differences were seen in
264 hypoglycemic symptomatology.

265 **Beta-Blockers:** Concomitant administration of propranolol (40 mg three times daily) and
266 glimepiride significantly increased C_{max}, AUC, and T_{1/2} of glimepiride by 23%, 22%, and 15%,
267 respectively, and it decreased CL/F by 18%. The recovery of M1 and M2 from urine, however,
268 did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal
269 subjects receiving propranolol and placebo. Pooled data from clinical trials in patients with
270 type 2 diabetes showed no evidence of clinically significant adverse interactions with
271 uncontrolled concurrent administration of beta-blockers. However, if beta-blockers are used,
272 caution should be exercised and patients should be warned about the potential for hypoglycemia.

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

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

284 **Other:** Although no specific interaction studies were performed, pooled data from clinical
285 trials showed no evidence of clinically significant adverse interactions with uncontrolled
286 concurrent administration of aspirin and other salicylates, H₂-receptor antagonists, ACE
287 inhibitors, calcium-channel blockers, estrogens, fibrates, NSAIDs, HMG CoA reductase
288 inhibitors, sulfonamides, or thyroid hormone.

289 **CLINICAL STUDIES**

290 **Drug-Naïve Patients with Type 2 Diabetes Mellitus:** In a 28-week, randomized, double-
291 blind clinical trial, 901 drug-naïve patients with type 2 diabetes inadequately controlled with diet
292 and exercise alone (baseline mean fasting plasma glucose [FPG] 211 mg/dL and baseline mean
293 HbA1c 9.1%) were started on AVANDARYL 4 mg/1 mg, rosiglitazone 4 mg, or glimepiride
294 1 mg. Doses could be increased at 4-week intervals to reach a target mean daily glucose of
295 ≤110 mg/dL. Patients who received AVANDARYL were randomized to 1 of 2 titration schemes
296 differing in the maximum total daily dose (4 mg/4 mg or 8 mg/4 mg). The maximum total daily
297 dose was 8 mg for rosiglitazone monotherapy and 4 mg for glimepiride monotherapy. All
298 treatments were administered as a once daily regimen. Improvements in FPG and HbA1c were

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

301

302 **Table 2. Glycemic Parameters in a 28-Week Study of AVANDARYL in Drug-Naïve**
 303 **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%

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

305 † Response is related to baseline HbA1c.

306

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

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

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

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

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

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

333

334 **Table 3. Glycemic Parameters in 24- to 26-Week Combination Studies of Rosiglitazone**
 335 **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 $\geq 0.7\%$ decrease from baseline	11%	36%	20%	68%

336 * p<0.0001 compared to sulfonylurea alone.
337

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

341 In a 2-year double-blind study, elderly patients (aged 59 to 89 years) on half-maximal
342 sulfonylurea (glipizide 10 mg twice daily) were randomized to the addition of rosiglitazone
343 (n = 115, 4 mg once daily to 8 mg as needed) or to continued up-titration of glipizide (n = 110),
344 to a maximum of 20 mg twice daily. Mean baseline FPG and HbA1c were 157 mg/dL and
345 7.72%, respectively, for the rosiglitazone plus glipizide arm and 159 mg/dL and 7.65%,
346 respectively, for the glipizide up-titration arm. Loss of glycemic control (FPG ≥ 180 mg/dL)
347 occurred in a significantly lower proportion of patients (2%) on rosiglitazone plus glipizide
348 compared to patients in the glipizide up-titration arm (28.7%). About 78% of the patients on
349 combination therapy completed the 2 years of therapy while only 51% completed on glipizide
350 monotherapy. The effect of combination therapy on FPG and HbA1c was durable over the 2-year
351 study period, with patients achieving a mean of 132 mg/dL for FPG and a mean of 6.98% for
352 HbA1c compared to no change on the glipizide arm.

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

358 **INDICATIONS AND USAGE**

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

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

368 **CONTRAINDICATIONS**

369 AVANDARYL is contraindicated in patients with:

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

373 **WARNINGS**

374 **Glimepiride:**

375 **SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY**

376 **The administration of oral hypoglycemic drugs has been reported to be associated with**
377 **increased cardiovascular mortality as compared to treatment with diet alone or diet plus**
378 **insulin. This warning is based on the study conducted by the University Group Diabetes**
379 **Program (UGDP), a long-term, prospective clinical trial designed to evaluate the**
380 **effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in**
381 **patients with non-insulin-dependent diabetes. The study involved 823 patients who were**
382 **randomly assigned to one of four treatment groups (*Diabetes* 1970;19[Suppl. 2]:747-830).**
383 **UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of**
384 **tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately**
385 **2½ times that of patients treated with diet alone. A significant increase in total mortality**
386 **was not observed, but the use of tolbutamide was discontinued based on the increase in**
387 **cardiovascular mortality, thus limiting the opportunity for the study to show an increase in**
388 **overall mortality. Despite controversy regarding the interpretation of these results, the**
389 **findings of the UGDP study provide an adequate basis for this warning. The patient should**
390 **be informed of the potential risks and advantages of glimepiride-containing tablets and of**
391 **alternative modes of therapy.**

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

396 **Rosiglitazone:**

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

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

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

414

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

	Placebo	Rosiglitazone
Events	N = 114 n (%)	N = 110 n (%)
Adjudicated		
Cardiovascular Deaths	4 (4)	5 (5)
CHF Worsening	4 (4)	7 (6)
– with overnight hospitalization	4 (4)	5 (5)
– without overnight hospitalization	0 (0)	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	5 (4)	10 (9)
– Myocardial Infarction	2 (2)	5 (5)
– Angina	3 (3)	6 (5)

418 * Includes hospitalization for any cardiovascular reason.

419

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

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

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

436 In a double-blind study in type 2 diabetes patients with chronic renal failure (112 received
437 4 mg or 8 mg of rosiglitazone plus insulin and 108 received insulin control), there was no
438 difference in cardiovascular adverse events with rosiglitazone in combination with insulin
439 compared to insulin control.

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

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

447 **PRECAUTIONS**

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

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

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

467 **Loss of Control of Blood Glucose:** When a patient stabilized on any antidiabetic regimen is
468 exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic
469 control may occur. At such times, it may be necessary to withhold AVANDARYL and
470 temporarily administer insulin. AVANDARYL may be reinstated after the acute episode is
471 resolved.

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

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

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

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

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

499

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

501

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

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

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

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

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

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

530 In pre-approval clinical studies in 4,598 patients treated with rosiglitazone, encompassing
531 approximately 3,600 patient years of exposure, there was no signal of drug-induced
532 hepatotoxicity or elevation of ALT levels. In the pre-approval controlled trials, 0.2% of patients
533 treated with rosiglitazone had elevations in ALT >3X the upper limit of normal compared to
534 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with
535 rosiglitazone were reversible and were not clearly causally related to therapy with rosiglitazone.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

617 **Rosiglitazone: Carcinogenesis:** A 2-year carcinogenicity study was conducted in
618 Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose
619 equivalent to approximately 12 times human AUC at the maximum recommended human daily
620 dose). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05 mg/kg/day,
621 0.3 mg/kg/day, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times
622 human AUC at the maximum recommended human daily dose for male and female rats,
623 respectively).

624 Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of
625 adipose hyperplasia in the mouse at doses ≥ 1.5 mg/kg/day (approximately 2 times human AUC
626 at the maximum recommended human daily dose). In rats, there was a significant increase in the
627 incidence of benign adipose tissue tumors (lipomas) at doses ≥ 0.3 mg/kg/day (approximately
628 2 times human AUC at the maximum recommended human daily dose). These proliferative
629 changes in both species are considered due to the persistent pharmacological overstimulation of
630 adipose tissue.

631 **Mutagenesis:** Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial
632 assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in
633 vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about
634 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic
635 activation.

636 **Impairment of Fertility:** Rosiglitazone had no effects on mating or fertility of male rats
637 given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended
638 human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility
639 (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and
640 estradiol (approximately 20 and 200 times human AUC at the maximum recommended human
641 daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times
642 human AUC at the maximum recommended human daily dose). In juvenile rats dosed from
643 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male
644 reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in
645 females (approximately 68 times human AUC at the maximum recommended daily dose). In
646 monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at
647 the maximum recommended human daily dose, respectively) diminished the follicular phase rise
648 in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal
649 phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct
650 inhibition of ovarian steroidogenesis.

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

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

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

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

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

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

682 **Pregnancy:** Pregnancy Category C. Because current information strongly suggests that
683 abnormal blood glucose levels during pregnancy are associated with a higher incidence of
684 congenital anomalies as well as increased neonatal morbidity and mortality, most experts
685 recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels
686 as close to normal as possible. AVANDARYL should not be used during pregnancy.

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

691 **Rosiglitazone:** There was no effect on implantation or the embryo with rosiglitazone
692 treatment during early pregnancy in rats, but treatment during mid-late gestation was associated
693 with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed
694 at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human
695 AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused
696 placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation
697 reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible
698 after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was
699 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately
700 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced
701 the number of uterine implantations and live offspring when juvenile female rats were treated at
702 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human
703 AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day
704 (approximately 4 times human AUC at the maximum recommended daily dose). There was no
705 effect on pre- or post-natal survival or growth.

706 **Glimepiride:** Glimepiride did not produce teratogenic effects in rats exposed orally up to
707 4,000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose
708 based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately
709 60 times the maximum recommended human dose based on surface area). Glimepiride has been
710 shown to be associated with intrauterine fetal death in rats when given in doses as low as
711 50 times the human dose based on surface area and in rabbits when given in doses as low as
712 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses
713 inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is
714 believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

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

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

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

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

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

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

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

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

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

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

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

762 **ADVERSE REACTIONS**

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

770 **Table 9. Adverse Events ($\geq 5\%$ in Any Treatment Group) Reported by Drug-Naïve Patients**
 771 **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

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

773
 774 Hypoglycemia was reported to be generally mild to moderate in intensity and none of the
 775 reported events of hypoglycemia resulted in withdrawal from the study. Hypoglycemia requiring
 776 parenteral treatment (i.e., intravenous glucose or glucagon injection) was observed in 3 (0.7%)
 777 patients treated with AVANDARYL.

778 Edema was reported by 3.2% of patients on AVANDARYL, 3.0% on rosiglitazone alone, and
 779 2.3% on glimepiride alone.

780 Congestive heart failure was observed in 1 (0.2%) patient treated with AVANDARYL and in
 781 1 (0.4%) patient treated with rosiglitazone monotherapy.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

849 **Human Ophthalmology Data:** Ophthalmic examinations were carried out in more than
850 500 subjects during long-term studies of glimepiride using the methodology of Taylor and West
851 and Laties et al. No significant differences were seen between glimepiride and glyburide in the
852 number of subjects with clinically important changes in visual acuity, intraocular tension, or in
853 any of the 5 lens-related variables examined. Ophthalmic examinations were carried out during
854 long-term studies using the method of Chylack et al. No significant or clinically meaningful
855 differences were seen between glimepiride and glipizide with respect to cataract progression by
856 subjective LOCS II grading and objective image analysis systems, visual acuity, intraocular
857 pressure, and general ophthalmic examination (see PRECAUTIONS, Animal Toxicology,
858 *Glimepiride*).

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

862 **OVERDOSAGE**

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

867 **Glimepiride:** Overdosage of sulfonylureas, including glimepiride, can produce hypoglycemia.
868 Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be
869 treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns.
870 Close monitoring should continue until the physician is assured that the patient is out of danger.
871 Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur
872 infrequently, but constitute medical emergencies requiring immediate hospitalization. If
873 hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid IV injection of
874 concentrated (50%) glucose solution. This should be followed by a continuous infusion of a
875 more dilute (10%) glucose solution at a rate that will maintain the blood glucose level above
876 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because
877 hypoglycemia may recur after apparent clinical recovery.

878 **DOSAGE AND ADMINISTRATION**

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

887 **Starting Dose:**

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

894 **Dose Titration:**

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

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

920 **Maximum Dose:**

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

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

928 **Specific Patient Populations:**

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

941 >2.5X upper limit of normal at start of therapy) (see PRECAUTIONS, Hepatic Effects and
942 CLINICAL PHARMACOLOGY, Special Populations, *Hepatic Impairment*). Liver enzyme
943 monitoring is recommended in all patients prior to initiation of therapy with AVANDARYL
944 and periodically thereafter (see PRECAUTIONS, Hepatic Effects).

945 **HOW SUPPLIED**

946 **Tablets:** Each tablet contains rosiglitazone as the maleate and glimepiride as follows:
947 4 mg/1 mg – yellow, rounded triangular tablet, gsk debossed on one side and 4/1 on the other.
948 4 mg/2 mg – orange, rounded triangular tablet, gsk debossed on one side and 4/2 on the other.
949 4 mg/4 mg – pink, rounded triangular tablet, gsk debossed on one side and 4/4 on the other.
950
951 4 mg/1 mg bottles of 30: NDC 0007-3151-13
952 4 mg/2 mg bottles of 30: NDC 0007-3152-13
953 4 mg/4 mg bottles of 30: NDC 0007-3153-13

954 **STORAGE**

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

957 **REFERENCES**

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

960



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968 Month 2006

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PATIENT INFORMATION

AVANDARYL™ (ah-VAN-duh-ri)

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.

35 **What should I tell my doctor before starting AVANDARYL?**

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

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

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

64 **How should I take AVANDARYL?**

- 65 • Take AVANDARYL by mouth once a day with your first main meal. Your doctor may need
66 to adjust your dose until your blood sugar is better controlled.
- 67 • It usually takes a few days for AVANDARYL to start lowering your blood sugar. It may take
68 2 to 3 months to see the full effect on your blood sugar level.
- 69 • If you miss a dose of AVANDARYL, take your pill as soon as you remember unless it is
70 time to take your next dose. Take your next dose at the usual time. Do not take a double dose
71 to make up for a missed dose.
- 72 • If you take too much AVANDARYL, call your doctor or poison control center right away.
73 Too much AVANDARYL can make your blood sugar level too low.

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

85 **What are possible serious side effects of AVANDARYL?**

86 **Talk to your doctor about these side effects:**

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

- 114 -nausea or vomiting
- 115 -stomach pain
- 116 -unusual or unexplained tiredness
- 117 -loss of appetite
- 118 -dark urine
- 119 -yellowing of your skin or the whites of your eyes

120

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

123 **How should I store AVANDARYL?**

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

128 **General information about AVANDARYL**

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

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

138 **What are the ingredients in AVANDARYL?**

139 **Active Ingredients:** rosiglitazone maleate and glimepiride.

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

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

146 4 mg/1 mg – yellow, rounded triangular tablet, “gsk” on one side and “4/1” on the other.

147 4 mg/2 mg – orange, rounded triangular tablet, “gsk” on one side and “4/2” on the other.

148 4 mg/4 mg – pink, rounded triangular tablet, “gsk” on one side and “4/4” on the other.

149

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151 AMARYL is a registered trademark of AVENTIS Pharmaceuticals Inc.

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

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