

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVANDARYL safely and effectively. See full prescribing information for AVANDARYL.

AVANDARYL (rosiglitazone maleate and glimepiride) tablets
Initial U.S. Approval: 2005

WARNING: CONGESTIVE HEART FAILURE

See full prescribing information for complete boxed warning.

- Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (5.2). After initiation of AVANDARYL, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDARYL must be considered.
- AVANDARYL is not recommended in patients with symptomatic heart failure. Initiation of AVANDARYL in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.2)

RECENT MAJOR CHANGES

| | |
|---|---------|
| Boxed Warning, AVANDIA-Rosiglitazone Medicines Access Program removal | 05/2014 |
| Indications and Usage, patient population restrictions removal (1) | 05/2014 |
| Dosage and Administration (2) | 05/2014 |
| Contraindications (4) | 05/2014 |
| Warnings and Precautions, Cardiac Failure (5.2) | 05/2014 |
| Warnings and Precautions, Major Adverse Cardiovascular Events (5.3) | 05/2014 |
| Warnings and Precautions, Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program removal (formerly 5.4) | 05/2014 |
| Warnings and Precautions, Weight Gain (5.6) | 05/2014 |

INDICATIONS AND USAGE

AVANDARYL is a combination antidiabetic product containing a thiazolidinedione and a sulfonylurea indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. (1)
Important Limitations of Use:

- Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. (1, 4)
- Coadministration with insulin is not recommended. (1, 5.2, 5.3)

DOSAGE AND ADMINISTRATION

- Individualize the starting dose based on the patient's current regimen. (2.1)
- Dose increases should be accompanied by careful monitoring for adverse events related to fluid retention. (2.2)
- Do not exceed the maximum recommended daily dose of 8 mg rosiglitazone and 4 mg glimepiride. (2.3)
- Do not initiate if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels. (2.4)

DOSAGE FORMS AND STRENGTHS

Rounded triangular tablets containing rosiglitazone/glimepiride: 4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg, 8 mg/2 mg, and 8 mg/4 mg (3)

CONTRAINDICATIONS

- Initiation in patients with established NYHA Class III or IV heart failure. (4)
- Hypersensitivity to rosiglitazone or any of the product's ingredients. (4)

WARNINGS and PRECAUTIONS

- One sulfonylurea has been shown to increase cardiovascular mortality; consider this risk when prescribing any sulfonylurea. (5.1)
- Fluid retention, which may exacerbate or lead to heart failure, may occur. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk of other cardiovascular effects. (5.2)
- Meta-analysis of 52 mostly short-term trials suggested a potential risk of ischemic cardiovascular (CV) events relative to placebo, not confirmed in a long-term CV outcome trial versus metformin or sulfonylurea. (5.3)
- Severe hypoglycemia may occur. Use particular care in elderly or debilitated patients and those with adrenal, pituitary, renal, or hepatic insufficiency. (5.4)
- Dose-related edema (5.5), weight gain (5.6), and anemia (5.10) may occur.
- Macular edema has been reported. (5.8)
- Increased incidence of bone fracture. (5.9)
- The glimepiride component may cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Consider a non-sulfonylurea alternative in these patients. (5.11)

ADVERSE REACTIONS

Common adverse reactions ($\geq 5\%$) reported in clinical trials for AVANDARYL without regard to causality were headache, hypoglycemia, and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Inhibitors of CYP2C8 (e.g., gemfibrozil) may increase rosiglitazone levels. (7.1)
- Inducers of CYP2C8 (e.g., rifampin) may decrease rosiglitazone levels. (7.1)
- Monitor patients for loss of control with drugs that cause hyperglycemia. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: No adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- Nursing Mothers: Discontinue drug or nursing (8.3)
- Safety and effectiveness in children younger than 18 years have not been established. (8.4)
- Elderly patients may be particularly susceptible to hypoglycemic effects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2014

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1 FULL PRESCRIBING INFORMATION

2 **WARNING: CONGESTIVE HEART FAILURE**

- 3 • **Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients [see Warnings and Precautions (5.2)]. After initiation of AVANDARYL, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDARYL must be considered.**
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- 10 • **AVANDARYL is not recommended in patients with symptomatic heart failure. Initiation of AVANDARYL in patients with established NYHA Class III or IV heart failure is contraindicated. [See Contraindications (4), Warnings and Precautions (5.2).]**
- 11
- 12

13 **1 INDICATIONS AND USAGE**

14 AVANDARYL[®] is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

15 **Important Limitations of Use:**

- 16 • Due to its mechanism of action, rosiglitazone is active only in the presence of endogenous insulin. Therefore, AVANDARYL should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
- 17
- 18
- 19
- 20 • Coadministration of AVANDARYL with insulin is not recommended [see Warnings and Precautions (5.2, 5.3)].
- 21

22 **2 DOSAGE AND ADMINISTRATION**

23 Therapy with AVANDARYL should be individualized for each patient. The risk-benefit of initiating monotherapy versus dual therapy with AVANDARYL should be considered.

24 No studies have been performed specifically examining the safety and efficacy of AVANDARYL in patients previously treated with other oral hypoglycemic agents and switched to AVANDARYL. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur. [See Indications and Usage (1).]

25 **2.1 Starting Dose**

26 The recommended starting dose is 4 mg/1 mg administered once daily with the first meal of the day. For adults already treated with a sulfonylurea or rosiglitazone, a starting dose of 4 mg/2 mg may be considered.

27 All patients should start the rosiglitazone component of AVANDARYL at the lowest recommended dose. Further increases in the dose of rosiglitazone should be accompanied by

36 careful monitoring for adverse events related to fluid retention [*see Boxed Warning, Warnings*
37 *and Precautions (5.2)*].

38 When switching from combination therapy of rosiglitazone plus glimepiride as separate
39 tablets, the usual starting dose of AVANDARYL is the dose of rosiglitazone and glimepiride
40 already being taken.

41 **2.2 Dose Titration**

42 Dose increases should be individualized according to the glycemic response of the
43 patient. Patients who may be more sensitive to glimepiride [*see Warnings and Precautions*
44 *(5.4)*], including the elderly, debilitated, or malnourished, and those with renal, hepatic, or
45 adrenal insufficiency, should be carefully titrated to avoid hypoglycemia. If hypoglycemia
46 occurs during up-titration of the dose or while maintained on therapy, a dosage reduction of the
47 glimepiride component of AVANDARYL may be considered. Increases in the dose of
48 rosiglitazone should be accompanied by careful monitoring for adverse events related to fluid
49 retention [*see Boxed Warning, Warnings and Precautions (5.2)*].

50 **To switch to AVANDARYL for adults currently treated with rosiglitazone**, dose
51 titration of the glimepiride component of AVANDARYL is recommended if patients are not
52 adequately controlled after 1 to 2 weeks. The glimepiride component may be increased in no
53 more than 2 mg increments. After an increase in the dosage of the glimepiride component, dose
54 titration of AVANDARYL is recommended if patients are not adequately controlled after 1 to 2
55 weeks.

56 **To switch to AVANDARYL for adults currently treated with sulfonylurea**, it may
57 take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of the
58 rosiglitazone component. Therefore, dose titration of the rosiglitazone component of
59 AVANDARYL is recommended if patients are not adequately controlled after 8 to 12 weeks.
60 Patients should be observed carefully (1 to 2 weeks) for hypoglycemia when being transferred
61 from longer half-life sulfonylureas (e.g., chlorpropamide) to AVANDARYL due to potential
62 overlapping of drug effect. After an increase in the dosage of the rosiglitazone component, dose
63 titration of AVANDARYL is recommended if patients are not adequately controlled after 2 to 3
64 months.

65 **2.3 Maximum Dose**

66 The maximum recommended daily dose is 8 mg rosiglitazone and 4 mg glimepiride.

67 **2.4 Specific Patient Populations**

68 Elderly and Malnourished Patients and Those With Renal, Hepatic, or Adrenal
69 Insufficiency: In elderly, debilitated, or malnourished patients, or in patients with renal, hepatic,
70 or adrenal insufficiency, the starting dose, dose increments, and maintenance dosage of
71 AVANDARYL should be conservative to avoid hypoglycemic reactions. [*See Warnings and*
72 *Precautions (5.4), Clinical Pharmacology (12.3).*]

73 Hepatic Impairment: Liver enzymes should be measured prior to initiating treatment
74 with AVANDARYL. Therapy with AVANDARYL should not be initiated if the patient exhibits
75 clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X

76 upper limit of normal at start of therapy). After initiation of AVANDARYL, liver enzymes
77 should be monitored periodically per the clinical judgment of the healthcare professional. [See
78 *Warnings and Precautions* (5.7), *Clinical Pharmacology* (12.3).]

79 **Pregnancy and Lactation:** AVANDARYL should not be used during pregnancy or in
80 nursing mothers.

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

84 **3 DOSAGE FORMS AND STRENGTHS**

85 Each rounded triangular tablet contains rosiglitazone maleate and glimepiride as follows:

- 86 • 4 mg/1 mg – yellow, gsk debossed on one side and 4/1 on the other.
- 87 • 4 mg/2 mg – orange, gsk debossed on one side and 4/2 on the other.
- 88 • 4 mg/4 mg – pink, gsk debossed on one side and 4/4 on the other.
- 89 • 8 mg/2 mg – pale pink, gsk debossed on one side and 8/2 on the other.
- 90 • 8 mg/4 mg – red, gsk debossed on one side and 8/4 on the other.

91 **4 CONTRAINDICATIONS**

92 Initiation of AVANDARYL in patients with established New York Heart Association
93 (NYHA) Class III or IV heart failure is contraindicated [see *Boxed Warning*].

94 AVANDARYL is contraindicated in patients with a history of a hypersensitivity reaction
95 to rosiglitazone or any of the product's ingredients.

96 **5 WARNINGS AND PRECAUTIONS**

97 **5.1 Increased Risk of Cardiovascular Mortality for Sulfonylurea Drugs**

98 The administration of oral hypoglycemic drugs has been reported to be associated
99 with increased cardiovascular mortality as compared with treatment with diet alone or diet
100 plus insulin. This warning is based on the trial conducted by the University Group Diabetes
101 Program (UGDP), a long-term, prospective clinical trial designed to evaluate the
102 effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in
103 patients with non-insulin-dependent diabetes. The trial involved 823 patients who were
104 randomly assigned to one of four treatment groups (*Diabetes* 1970;19[Suppl. 2]:747-830).
105 UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of
106 tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately
107 2½ times that of patients treated with diet alone. A significant increase in total mortality
108 was not observed, but the use of tolbutamide was discontinued based on the increase in
109 cardiovascular mortality, thus limiting the opportunity for the trial to show an increase in
110 overall mortality. Despite controversy regarding the interpretation of these results, the
111 findings of the UGDP trial provide an adequate basis for this warning. The patient should
112 be informed of the potential risks and advantages of glimepiride-containing tablets and of
113 alternative modes of therapy.

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

118 **5.2 Cardiac Failure With Rosiglitazone**

119 Rosiglitazone, like other thiazolidinediones, alone or in combination with other
120 antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure.
121 Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms
122 develop, the heart failure should be managed according to current standards of care.
123 Furthermore, discontinuation or dose reduction of rosiglitazone must be considered [*see Boxed*
124 *Warning*].

125 Patients with congestive heart failure (CHF) NYHA Class I and II treated with
126 rosiglitazone have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-
127 controlled, echocardiographic trial was conducted in 224 patients with type 2 diabetes mellitus
128 and NYHA Class I or II CHF (ejection fraction $\leq 45\%$) on background antidiabetic and CHF
129 therapy. An independent committee conducted a blinded evaluation of fluid-related events
130 (including congestive heart failure) and cardiovascular hospitalizations according to predefined
131 criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were
132 reported by investigators. Although no treatment difference in change from baseline of ejection
133 fractions was observed, more cardiovascular adverse events were observed with rosiglitazone
134 treatment compared with placebo during the 52-week trial. (See Table 1.)

135

136 **Table 1. Emergent Cardiovascular Adverse Events in Patients With Congestive Heart**
 137 **Failure (NYHA Class I and II) Treated With Rosiglitazone or Placebo (in Addition to**
 138 **Background Antidiabetic and CHF Therapy)**

| Events | Rosiglitazone N = 110 n (%) | Placebo N = 114 n (%) |
|---|-----------------------------------|-----------------------------|
| Adjudicated | | |
| Cardiovascular deaths | 5 (5%) | 4 (4%) |
| CHF worsening | 7 (6%) | 4 (4%) |
| – with overnight hospitalization | 5 (5%) | 4 (4%) |
| – without overnight hospitalization | 2 (2%) | 0 (0%) |
| New or worsening edema | 28 (25%) | 10 (9%) |
| New or worsening dyspnea | 29 (26%) | 19 (17%) |
| Increases in CHF medication | 36 (33%) | 20 (18%) |
| Cardiovascular hospitalization ^a | 21 (19%) | 15 (13%) |
| Investigator-reported, non-adjudicated | | |
| Ischemic adverse events | 10 (9%) | 5 (4%) |
| – Myocardial infarction | 5 (5%) | 2 (2%) |
| – Angina | 6 (5%) | 3 (3%) |

139 ^a Includes hospitalization for any cardiovascular reason.

140
 141 In a long-term, cardiovascular outcome trial (RECORD) in patients with type 2 diabetes
 142 [see Adverse Reactions (6.1)], the incidence of heart failure was higher in patients treated with
 143 rosiglitazone [2.7% (61/2,220) compared with active control 1.3% (29/2,227), HR 2.10 (95% CI:
 144 1.35, 3.27)].

145 Initiation of AVANDARYL in patients with established NYHA Class III or IV heart
 146 failure is contraindicated. AVANDARYL is not recommended in patients with symptomatic
 147 heart failure. [See Boxed Warning.]

148 Patients experiencing acute coronary syndromes have not been studied in controlled
 149 clinical trials. In view of the potential for development of heart failure in patients having an acute
 150 coronary event, initiation of AVANDARYL is not recommended for patients experiencing an
 151 acute coronary event, and discontinuation of AVANDARYL during this acute phase should be
 152 considered.

153 Patients with NYHA Class III and IV cardiac status (with or without CHF) have not been
 154 studied in controlled clinical trials. AVANDARYL is not recommended in patients with NYHA
 155 Class III and IV cardiac status.

156 **Congestive Heart Failure During Coadministration of Rosiglitazone With Insulin:**
 157 In trials in which rosiglitazone was added to insulin, rosiglitazone increased the risk of
 158 congestive heart failure. Coadministration of rosiglitazone and insulin is not recommended. [See
 159 *Indications and Usage (1), Warnings and Precautions (5.3).*]

160 In 7 controlled, randomized, double-blind trials which had durations from 16 to 26 weeks
161 and which were included in a meta-analysis [*see Warnings and Precautions (5.3)*], patients with
162 type 2 diabetes mellitus were randomized to coadministration of rosiglitazone and insulin
163 (N = 1,018) or insulin (N = 815). In these 7 trials, rosiglitazone was added to insulin. These trials
164 included patients with long-standing diabetes (median duration of 12 years) and a high
165 prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy,
166 ischemic heart disease, vascular disease, and congestive heart failure. The total number of
167 patients with emergent congestive heart failure was 23 (2.3%) and 8 (1.0%) in the rosiglitazone
168 plus insulin and insulin groups, respectively.

169 Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing
170 Rosiglitazone to Pioglitazone: Three observational studies in elderly diabetic patients (age 65
171 years and older) found that rosiglitazone statistically significantly increased the risk of
172 hospitalized heart failure compared to use of pioglitazone. One other observational study in
173 patients with a mean age of 54 years, which also included an analysis in a subpopulation of
174 patients >65 years of age, found no statistically significant increase in emergency department
175 visits or hospitalization for heart failure in patients treated with rosiglitazone compared to
176 pioglitazone in the older subgroup.

177 **5.3 Major Adverse Cardiovascular Events**

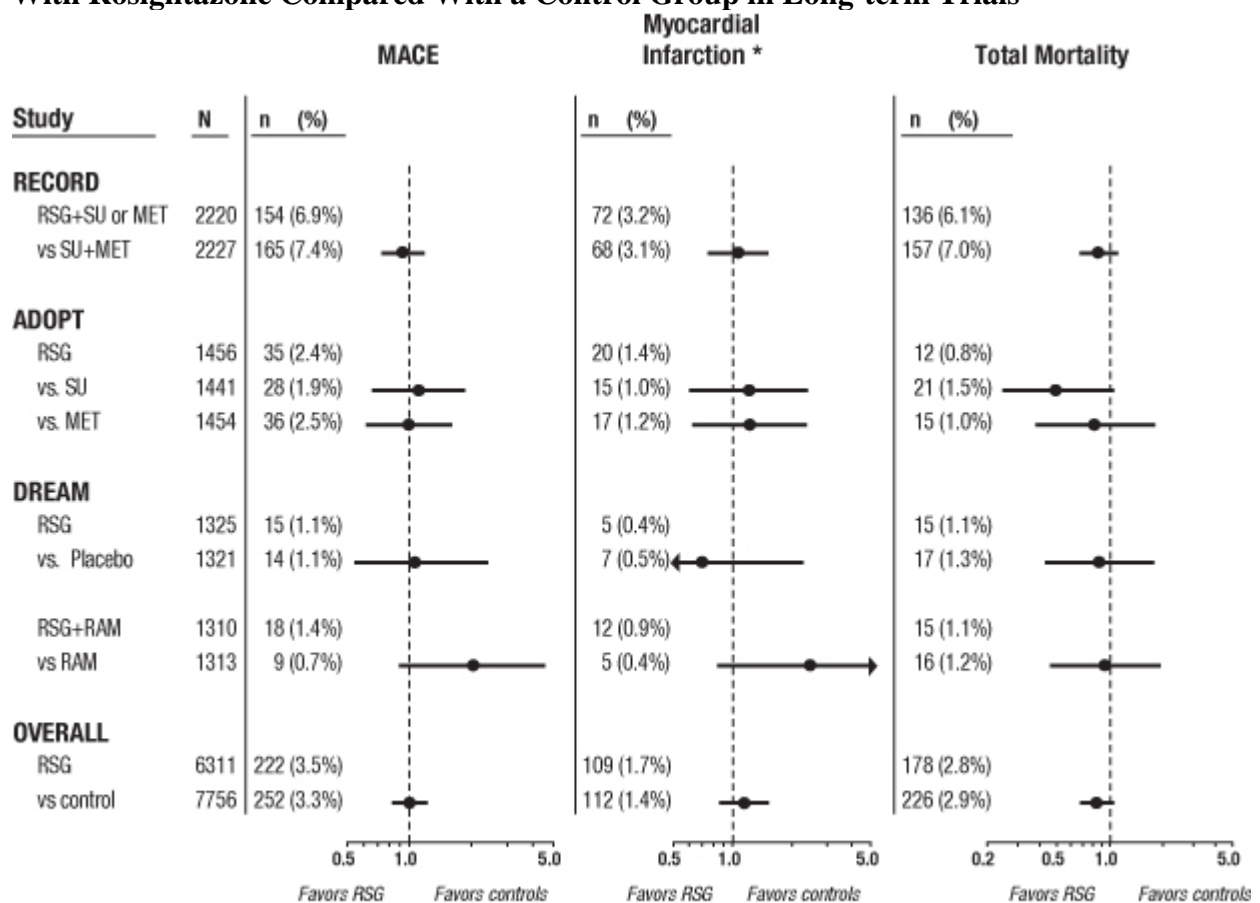
178 Data from long-term, prospective, randomized, controlled clinical trials of rosiglitazone
179 versus metformin or sulfonylureas, particularly a cardiovascular outcome trial (RECORD),
180 observed no difference in overall mortality or in major adverse cardiovascular events (MACE)
181 and its components. A meta-analysis of mostly short-term trials suggested an increased risk for
182 myocardial infarction with rosiglitazone compared with placebo.

183 Cardiovascular Events in Large, Long-term, Prospective, Randomized,
184 Controlled Trials of Rosiglitazone: RECORD, a prospectively designed cardiovascular
185 outcome trial (mean follow-up 5.5 years; 4,447 patients), compared the addition of rosiglitazone
186 to metformin or a sulfonylurea (N = 2,220) with a control group of metformin plus sulfonylurea
187 (N = 2,227) in patients with type 2 diabetes [*see Adverse Reactions (6.1)*]. Non-inferiority was
188 demonstrated for the primary endpoint, cardiovascular hospitalization or cardiovascular death,
189 for rosiglitazone compared with control [HR 0.99 (95% CI: 0.85, 1.16)] demonstrating no overall
190 increased risk in cardiovascular morbidity or mortality. The hazard ratios for total mortality and
191 MACE were consistent with the primary endpoint and the 95% CI similarly excluded a 20%
192 increase in risk for rosiglitazone. The hazard ratios for the components of MACE were 0.72
193 (95% CI: 0.49, 1.06) for stroke, 1.14 (95% CI: 0.80, 1.63) for myocardial infarction, and 0.84
194 (95% CI: 0.59, 1.18) for cardiovascular death.

195 The results of RECORD are consistent with the findings of 2 earlier long-term,
196 prospective, randomized, controlled clinical trials (each trial >3 years' duration; total of 9,620
197 patients) (see Figure 1). In patients with impaired glucose tolerance (DREAM trial), although the
198 incidence of cardiovascular events was higher among subjects who were randomized to
199 rosiglitazone in combination with ramipril than among subjects randomized to ramipril alone, no

200 statistically significant differences were observed for MACE and its components between
 201 rosiglitazone and placebo. In type 2 diabetes patients who were initiating oral agent monotherapy
 202 (ADOPT trial), no statistically significant differences were observed for MACE and its
 203 components between rosiglitazone and metformin or a sulfonylurea.
 204

205 **Figure 1. Hazard Ratios for the Risk of MACE, Myocardial Infarction, and Total Mortality**
 206 **With Rosiglitazone Compared With a Control Group in Long-term Trials**



RSG = rosiglitazone; SU = sulfonylurea; MET = metformin; RAM = ramipril
 * Myocardial infarction includes fatal and non-fatal MI plus sudden death

207
 208
 209 **Cardiovascular Events in a Group of 52 Clinical Trials:** In a meta-analysis of 52
 210 double-blind, randomized, controlled clinical trials designed to assess glucose-lowering efficacy
 211 in type 2 diabetes (mean duration 6 months), a statistically significant increased risk of
 212 myocardial infarction with rosiglitazone versus pooled comparators was observed [0.4% versus
 213 0.3%; OR 1.8, (95% CI: 1.03, 3.25)]. A statistically non-significant increased risk of MACE was
 214 observed with rosiglitazone versus pooled comparators (OR 1.44, 95% CI: 0.95, 2.20). In the
 215 placebo-controlled trials, a statistically significant increased risk of myocardial infarction [0.4%
 216 versus 0.2%, OR 2.23 (95% CI: 1.14, 4.64)] and statistically non-significant increased risk of

217 MACE [0.7% versus 0.5%, OR 1.53 (95% CI: 0.94, 2.54)] with rosiglitazone ~~were~~ **was** observed.
218 In the active-controlled trials, there was no increased risk of myocardial infarction or MACE.

219 Mortality in Observational Studies of Rosiglitazone Compared to Pioglitazone:

220 Three observational studies in elderly diabetic patients (age 65 years and older) found that
221 rosiglitazone statistically significantly increased the risk of all-cause mortality compared to use
222 of pioglitazone. One observational study in patients with a mean age of 54 years found no
223 difference in all-cause mortality between patients treated with rosiglitazone compared to
224 pioglitazone and reported similar results in the subpopulation of patients >65 years of age. One
225 additional small, prospective, observational study found no statistically significant differences
226 for CV mortality and all-cause mortality in patients treated with rosiglitazone compared to
227 pioglitazone.

228 **5.4 Hypoglycemia**

229 AVANDARYL is a combination tablet containing rosiglitazone and glimepiride, a
230 sulfonylurea. All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper
231 patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Elderly
232 patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs.
233 Debilitated or malnourished patients, and those with adrenal, pituitary, renal, or hepatic
234 insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs.
235 A starting dose of 1 mg glimepiride, as contained in AVANDARYL 4 mg/1 mg, followed by
236 appropriate dose titration is recommended in these patients. [See *Clinical Pharmacology (12.3)*.]
237 Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-
238 adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur
239 when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or
240 when more than one glucose-lowering drug is used.

241 Patients receiving rosiglitazone in combination with a sulfonylurea may be at risk for
242 hypoglycemia, and a reduction in the dose of the sulfonylurea may be necessary [see *Dosage and*
243 *Administration (2.2)*].

244 **5.5 Edema**

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

248 Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can
249 exacerbate or lead to congestive heart failure, AVANDARYL should be used with caution in
250 patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart
251 failure [see *Boxed Warning, Warnings and Precautions (5.2)*, *Patient Counseling Information*
252 *(17.1)*].

253 In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was
254 reported in patients treated with rosiglitazone, and may be dose-related. Patients with ongoing
255 edema were more likely to have adverse events associated with edema if started on combination

256 therapy with insulin and rosiglitazone [see Adverse Reactions (6.1)]. The use of AVANDARYL
 257 in combination with insulin is not recommended [see Warnings and Precautions (5.2, 5.3)].

258 5.6 Weight Gain

259 Dose-related weight gain was seen with AVANDARYL, rosiglitazone alone, and
 260 rosiglitazone together with other hypoglycemic agents (see Table 2). The mechanism of weight
 261 gain is unclear but probably involves a combination of fluid retention and fat accumulation.

262

263 **Table 2. Weight Changes (kg) From Baseline at Endpoint During Clinical Trials**

[Median (25th, 75th Percentiles)]

| 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 | | | | |
| Duration | Control Group | Rosiglitazone + Control Therapy | | |
| | | | 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 Patients With Inadequate Control on Diet and Exercise | | | | |
| Duration | Control Group | | 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 | | |

264

265 In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed
 266 with type 2 diabetes not previously treated with antidiabetic medication, the median weight
 267 change (25th, 75th percentiles) from baseline at 4 years was 3.5 kg (0.0, 8.1) for rosiglitazone,
 268 2.0 kg (-1.0, 4.8) for glyburide, and -2.4 kg (-5.4, 0.5) for metformin.

269 In postmarketing experience with rosiglitazone alone or in combination with other
 270 hypoglycemic agents, there have been rare reports of unusually rapid increases in weight and
 271 increases in excess of that generally observed in clinical trials. Patients who experience such

272 increases should be assessed for fluid accumulation and volume-related events such as excessive
273 edema and congestive heart failure [see *Boxed Warning*].

274 **5.7 Hepatic Effects**

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

278 Liver enzymes should be measured prior to the initiation of therapy with AVANDARYL
279 in all patients and periodically thereafter per the clinical judgment of the healthcare professional.
280 Therapy with AVANDARYL should not be initiated in patients with increased baseline liver
281 enzyme levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes
282 (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with AVANDARYL
283 should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or
284 continuation of, therapy with AVANDARYL in patients with mild liver enzyme elevations
285 should proceed with caution and include close clinical follow-up, including more frequent liver
286 enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time
287 ALT levels increase to >3X the upper limit of normal in patients on therapy with
288 AVANDARYL, liver enzyme levels should be rechecked as soon as possible. If ALT levels
289 remain >3X the upper limit of normal, therapy with AVANDARYL should be discontinued.

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

295 **5.8 Macular Edema**

296 Macular edema has been reported in postmarketing experience in some diabetic patients
297 who were taking rosiglitazone or another thiazolidinedione. Some patients presented with blurred
298 vision or decreased visual acuity, but some patients appear to have been diagnosed on routine
299 ophthalmologic examination. Most patients had peripheral edema at the time macular edema was
300 diagnosed. Some patients had improvement in their macular edema after discontinuation of their
301 thiazolidinedione. Patients with diabetes should have regular eye exams by an ophthalmologist,
302 per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who
303 reports any kind of visual symptom should be promptly referred to an ophthalmologist,
304 regardless of the patient's underlying medications or other physical findings. [See *Adverse*
305 *Reactions (6.3)*.]

306 **5.9 Fractures**

307 Long-term trials (ADOPT and RECORD) show an increased incidence of bone fracture
308 in patients, particularly female patients, taking rosiglitazone [see *Adverse Reactions (6.1)*]. This
309 increased incidence was noted after the first year of treatment and persisted during the course of
310 the trial. The majority of the fractures in the women who received rosiglitazone occurred in the
311 upper arm, hand, and foot. These sites of fracture are different from those usually associated with

312 postmenopausal osteoporosis (e.g., hip or spine). Other trials suggest that this risk may also
313 apply to men, although the risk of fracture among women appears higher than that among men.
314 The risk of fracture should be considered in the care of patients treated with rosiglitazone, and
315 attention given to assessing and maintaining bone health according to current standards of care.

316 **5.10 Hematologic Effects**

317 Decreases in hemoglobin and hematocrit occurred in a dose-related fashion in adult
318 patients treated with rosiglitazone [*see Adverse Reactions (6.2)*]. The observed changes may be
319 related to the increased plasma volume observed with treatment with rosiglitazone.

320 **5.11 Hemolytic Anemia**

321 Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with
322 sulfonylurea agents can lead to hemolytic anemia. Because glimepiride, a component of
323 AVANDARYL, belongs to the class of sulfonylurea agents, caution should be used in patients
324 with G6PD deficiency and a non-sulfonylurea alternative should be considered. In postmarketing
325 experience, hemolytic anemia has also been reported in patients receiving sulfonylureas who did
326 not have known G6PD deficiency [*see Adverse Reactions (6.1)*].

327 **5.12 Diabetes and Blood Glucose Control**

328 When a patient stabilized on any antidiabetic regimen is exposed to stress such as fever,
329 trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it
330 may be necessary to withhold AVANDARYL and temporarily administer insulin.
331 AVANDARYL may be reinstated after the acute episode is resolved.

332 Periodic fasting glucose and HbA1c measurements should be performed to monitor
333 therapeutic response.

334 **5.13 Ovulation**

335 Therapy with rosiglitazone, like other thiazolidinediones, may result in ovulation in some
336 premenopausal anovulatory women. As a result, these patients may be at an increased risk for
337 pregnancy while taking rosiglitazone [*see Use in Specific Populations (8.1)*]. Thus, adequate
338 contraception in premenopausal women should be recommended. This possible effect has not
339 been specifically investigated in clinical trials; therefore the frequency of this occurrence is not
340 known.

341 Although hormonal imbalance has been seen in preclinical studies [*see Nonclinical*
342 *Toxicology (13.1)*], the clinical significance of this finding is not known. If unexpected menstrual
343 dysfunction occurs, the benefits of continued therapy with AVANDARYL should be reviewed.

344 **6 ADVERSE REACTIONS**

345 The following adverse reactions are discussed in more detail elsewhere in the labeling:

- 346 • Increased Risk of Cardiovascular Mortality for Sulfonylurea Drugs [*see Warnings and*
347 *Precautions (5.13)*]
- 348 • Cardiac Failure With Rosiglitazone [*see Warnings and Precautions (5.1)*]
- 349 • Major Adverse Cardiovascular Events [*see Warnings and Precautions (5.2)*]
- 350 • Hypoglycemia [*see Warnings and Precautions (5.4)*]

- 351 • Edema [see Warnings and Precautions (5.5)]
- 352 • Weight Gain [see Warnings and Precautions (5.6)]
- 353 • Hepatic Effects [see Warnings and Precautions (5.7)]
- 354 • Macular Edema [see Warnings and Precautions (5.8)]
- 355 • Fractures [see Warnings and Precautions (5.9)]
- 356 • Hematologic Effects [see Warnings and Precautions (5.10)]
- 357 • Hemolytic Anemia [see Warnings and Precautions (5.11)]
- 358 • Ovulation [see Warnings and Precautions (5.13)]

359 **6.1 Clinical Trial Experience**

360 Because clinical trials are conducted under widely varying conditions, adverse reaction
 361 rates observed in the clinical trials of a drug cannot be directly compared with rates in the
 362 clinical trials of another drug and may not reflect the rates observed in practice.

363 Patients With Inadequate Glycemic Control on Diet and Exercise: Table 3
 364 summarizes adverse events occurring at a frequency of $\geq 5\%$ in any treatment group in the
 365 28-week, double-blind trial of AVANDARYL in patients with type 2 diabetes mellitus
 366 inadequately controlled on diet and exercise. Patients in this trial were started on AVANDARYL
 367 4 mg/1 mg, rosiglitazone 4 mg, or glimepiride 1 mg. Doses could be increased at 4-week
 368 intervals to reach a maximum total daily dose of either 4 mg/4 mg or 8 mg/4 mg for
 369 AVANDARYL, 8 mg for rosiglitazone monotherapy, or 4 mg for glimepiride monotherapy.

371 **Table 3. Adverse Events ($\geq 5\%$ in any Treatment Group) Reported by Patients With**
 372 **Inadequate Glycemic Control on Diet and Exercise in a 28-Week, Double-blind Clinical**
 373 **Trial of AVANDARYL**

| | Glimepiride Monotherapy N = 222 | Rosiglitazone Monotherapy N = 230 | AVANDARYL 4 mg/4 mg N = 224 | AVANDARYL 8 mg/4 mg N = 218 |
|---------------------------|--|--|--|--|
| Preferred Term | % | % | % | % |
| 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 ^a | 4.1 | 0.4 | 3.6 | 5.5 |

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

375
 376 Hypoglycemia was reported to be generally mild to moderate in intensity and none of the
 377 reported events of hypoglycemia resulted in withdrawal from the trial. Hypoglycemia requiring
 378 parenteral treatment (i.e., intravenous glucose or glucagon injection) was observed in 3 (0.7%)
 379 patients treated with AVANDARYL.

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

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

384 Patients Treated With Rosiglitazone Added to Sulfonylurea Monotherapy and
385 Other Experience With Rosiglitazone or Glimepiride: Trials utilizing rosiglitazone in
386 combination with a sulfonylurea provide support for the use of AVANDARYL. Adverse event
387 data from these trials, in addition to adverse events reported with the use of rosiglitazone and
388 glimepiride therapy, are presented below.

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

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

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

407 In 26-week, double-blind, fixed-dose trials, edema was reported with higher frequency in
408 the rosiglitazone plus insulin combination trials (insulin, 5.4%; and rosiglitazone in combination
409 with insulin, 14.7%). Reports of new onset or exacerbation of congestive heart failure occurred
410 at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with
411 rosiglitazone [see *Boxed Warning, Warnings and Precautions (5.2)*].

412 *Glimepiride: Hypoglycemia:* The incidence of hypoglycemia with glimepiride, as
413 documented by blood glucose values < 60 mg/dL, ranged from 0.9% to 1.7% in 2 large, well-
414 controlled, 1-year trials. In patients treated with glimepiride in US placebo-controlled trials
415 (N = 746), adverse events, other than hypoglycemia, considered to be possibly or probably
416 related to trial drug that occurred in more than 1% of patients included dizziness (1.7%), asthenia
417 (1.6%), headache (1.5%), and nausea (1.1%).

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

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

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

429 *Hematologic Reactions:* Leukopenia, agranulocytosis, thrombocytopenia,
430 hemolytic anemia [see *Warnings and Precautions (5.11)*], aplastic anemia, and pancytopenia
431 have been reported with sulfonylureas, including glimepiride.

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

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

445 *Human Ophthalmology Data:* Ophthalmic examinations were carried out in more
446 than 500 subjects during long-term trials of glimepiride using the methodology of Taylor and
447 West and Laties et al. No significant differences were seen between glimepiride and glyburide in
448 the number of subjects with clinically important changes in visual acuity, intraocular tension, or
449 in any of the 5 lens-related variables examined. Ophthalmic examinations were carried out
450 during long-term trials using the method of Chylack et al. No significant or clinically meaningful
451 differences were seen between glimepiride and glipizide with respect to cataract progression by
452 subjective LOCS II grading and objective image analysis systems, visual acuity, intraocular
453 pressure, and general ophthalmic examination [see *Nonclinical Toxicology (13.2)*].

454 Long-term Trial of Rosiglitazone as Monotherapy: A 4- to 6-year trial (ADOPT)
455 compared the use of rosiglitazone (n = 1,456), glyburide (n = 1,441), and metformin (n = 1,454)
456 as monotherapy in patients recently diagnosed with type 2 diabetes who were not previously
457 treated with antidiabetic medication. Table 4 presents adverse reactions without regard to
458 causality; rates are expressed per 100 patient-years (PY) exposure to account for the differences
459 in exposure to trial medication across the 3 treatment groups.

460 In ADOPT, fractures were reported in a greater number of women treated with
 461 rosiglitazone (9.3%, 2.7/100 patient-years) compared with glyburide (3.5%, 1.3/100 patient-
 462 years) or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women
 463 who received rosiglitazone were reported in the upper arm, hand, and foot. [See Warnings and
 464 Precautions (5.9).] The observed incidence of fractures for male patients was similar among the
 465 3 treatment groups.

467 **Table 4. On-therapy Adverse Events [≥ 5 Events/100 Patient-Years (PY)] in any Treatment**
 468 **Group Reported in a 4- to 6-Year Clinical Trial of Rosiglitazone as Monotherapy (ADOPT)**

| Preferred Term | Rosiglitazone N = 1,456 PY = 4,954 | Glyburide N = 1,441 PY = 4,244 | Metformin N = 1,454 PY = 4,906 |
|-----------------------------------|--|--------------------------------------|--------------------------------------|
| Nasopharyngitis | 6.3 | 6.9 | 6.6 |
| Back pain | 5.1 | 4.9 | 5.3 |
| Arthralgia | 5.0 | 4.8 | 4.2 |
| Hypertension | 4.4 | 6.0 | 6.1 |
| Upper respiratory tract infection | 4.3 | 5.0 | 4.7 |
| Hypoglycemia | 2.9 | 13.0 | 3.4 |
| Diarrhea | 2.5 | 3.2 | 6.8 |

469
 470 *Long-term Trial of Rosiglitazone as Combination Therapy (RECORD):*
 471 RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in
 472 Diabetes) was a multicenter, randomized, open-label, non-inferiority trial in subjects with type 2
 473 diabetes inadequately controlled on maximum doses of metformin or sulfonylurea (glyburide,
 474 gliclazide, or glimepiride) to compare the time to reach the combined cardiovascular endpoint of
 475 cardiovascular death or cardiovascular hospitalization between patients randomized to the
 476 addition of rosiglitazone versus metformin or sulfonylurea. The trial included patients who have
 477 failed metformin or sulfonylurea monotherapy; those who failed metformin (n = 2,222) were
 478 randomized to receive either add-on rosiglitazone (n = 1,117) or add-on sulfonylurea (n = 1,105),
 479 and those who failed sulfonylurea (n = 2,225) were randomized to receive either add-on
 480 rosiglitazone (n = 1,103) or add-on metformin (n = 1,122). Patients were treated to target HbA1c
 481 $\leq 7\%$ throughout the trial.

482 The mean age of patients in this trial was 58 years, 52% were male, and the mean
 483 duration of follow-up was 5.5 years. Rosiglitazone demonstrated non-inferiority to active control
 484 for the primary endpoint of cardiovascular hospitalization or cardiovascular death (HR 0.99, 95%
 485 CI: 0.85-1.16). There were no significant differences between groups for secondary endpoints
 486 with the exception of congestive heart failure (see Table 5). The incidence of congestive heart
 487 failure was significantly greater among patients randomized to rosiglitazone.

488

489 **Table 5. Cardiovascular (CV) Outcomes for the RECORD Trial**

| Primary Endpoint | Rosiglitazone N = 2,220 | Active Control N = 2,227 | Hazard Ratio | 95% CI |
|--|------------------------------------|-------------------------------------|-------------------------|---------------|
| CV death or CV hospitalization | 321 | 323 | 0.99 | 0.85-1.16 |
| Secondary Endpoint | | | | |
| All-cause death | 136 | 157 | 0.86 | 0.68-1.08 |
| CV death | 60 | 71 | 0.84 | 0.59-1.18 |
| Myocardial infarction | 64 | 56 | 1.14 | 0.80-1.63 |
| Stroke | 46 | 63 | 0.72 | 0.49-1.06 |
| CV death, myocardial infarction, or stroke | 154 | 165 | 0.93 | 0.74-1.15 |
| Heart failure | 61 | 29 | 2.10 | 1.35-3.27 |

490
 491 There was an increased incidence of bone fracture for subjects randomized to
 492 rosiglitazone in addition to metformin or sulfonylurea compared with those randomized to
 493 metformin plus sulfonylurea (8.3% versus 5.3%) [see *Warnings and Precautions (5.9)*]. The
 494 majority of fractures were reported in the upper limbs and distal lower limbs. The risk of fracture
 495 appeared to be higher in females relative to control (11.5% versus 6.3%), than in males relative
 496 to control (5.3% versus 4.3%). Additional data are necessary to determine whether there is an
 497 increased risk of fracture in males after a longer period of follow-up.

498 **6.2 Laboratory Abnormalities**

499 Rosiglitazone: Hematologic: Decreases in mean hemoglobin and hematocrit occurred
 500 in a dose-related fashion in adult patients treated with rosiglitazone (mean decreases in
 501 individual trials as much as 1.0 g/dL hemoglobin and as much as 3.3% hematocrit). The changes
 502 occurred primarily during the first 3 months following initiation of therapy with rosiglitazone or
 503 following a dose increase in rosiglitazone. The time course and magnitude of decreases were
 504 similar in patients treated with a combination of rosiglitazone and other hypoglycemic agents or
 505 monotherapy with rosiglitazone. White blood cell counts also decreased slightly in adult patients
 506 treated with rosiglitazone. Decreases in hematologic parameters may be related to increased
 507 plasma volume observed with treatment with rosiglitazone.

508 Lipids: Changes in serum lipids have been observed following treatment with
 509 rosiglitazone in adults [see *Clinical Pharmacology (12.2)*].

510 Serum Transaminase Levels: In pre-approval clinical trials in 4,598 patients treated
 511 with rosiglitazone encompassing approximately 3,600 patient-years of exposure, there was no
 512 evidence of drug-induced hepatotoxicity.

513 In pre-approval controlled trials, 0.2% of patients treated with rosiglitazone had
 514 reversible elevations in ALT >3X the upper limit of normal compared with 0.2% on placebo and
 515 0.5% on active comparators. The ALT elevations in patients treated with rosiglitazone were
 516 reversible. Hyperbilirubinemia was found in 0.3% of patients treated with rosiglitazone
 517 compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In

518 pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic
519 failure. [See *Warnings and Precautions (5.7)*.]

520 In the 4- to 6-year ADOPT trial, patients treated with rosiglitazone (4,954 patient-years
521 exposure), glyburide (4,244 patient-years exposure), or metformin (4,906 patient-years exposure)
522 as monotherapy had the same rate of ALT increase to >3X upper limit of normal (0.3 per 100
523 patient-years exposure).

524 In the RECORD trial, patients randomized to rosiglitazone in addition to metformin or
525 sulfonylurea (10,849 patient-years exposure) and to metformin plus sulfonylurea (10,209 patient-
526 years exposure) had a rate of ALT increase to $\geq 3X$ upper limit of normal of approximately 0.2
527 and 0.3 per 100 patient-years exposure, respectively.

528 **6.3 Postmarketing Experience**

529 In addition to adverse reactions reported from clinical trials, the events described below
530 have been identified during post-approval use of AVANDARYL or its individual components.
531 Because these events are reported voluntarily from a population of unknown size, it is not
532 possible to reliably estimate their frequency or to always establish a causal relationship to drug
533 exposure.

534 In patients receiving thiazolidinedione therapy, serious adverse events with or without a
535 fatal outcome, potentially related to volume expansion (e.g., congestive heart failure, pulmonary
536 edema, and pleural effusions) have been reported [see *Boxed Warning, Warnings and*
537 *Precautions (5.2)*].

538 There are postmarketing reports with rosiglitazone of hepatitis, hepatic enzyme
539 elevations to 3 or more times the upper limit of normal, and hepatic failure with and without fatal
540 outcome, although causality has not been established.

541 There are postmarketing reports with rosiglitazone of rash, pruritus, urticaria,
542 angioedema, anaphylactic reaction, Stevens-Johnson syndrome [see *Contraindications (4)*], and
543 new onset or worsening diabetic macular edema with decreased visual acuity [see *Warnings and*
544 *Precautions (5.8)*].

545 **7 DRUG INTERACTIONS**

546 **7.1 Drugs Metabolized by Cytochrome P450**

547 An inhibitor of CYP2C8 (e.g., gemfibrozil) may increase the AUC of rosiglitazone and
548 an inducer of CYP2C8 (e.g., rifampin) may decrease the AUC of rosiglitazone. Therefore, if an
549 inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone,
550 changes in diabetes treatment may be needed based upon clinical response. [See *Clinical*
551 *Pharmacology (12.4)*.]

552 A potential interaction between oral miconazole and oral hypoglycemic agents leading to
553 severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical,
554 or vaginal preparations of miconazole is not known. Potential interactions of glimepiride with
555 other drugs metabolized by cytochrome P450 2C9 also include phenytoin, diclofenac, ibuprofen,
556 naproxen, and mefenamic acid. [See *Clinical Pharmacology (12.4)*.]

557 **7.2 Drugs That Produce Hyperglycemia**

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

564 **8 USE IN SPECIFIC POPULATIONS**

565 **8.1 Pregnancy**

566 Pregnancy Category C.

567 All pregnancies have a background risk of birth defects, loss, or other adverse outcome
568 regardless of drug exposure. This background risk is increased in pregnancies complicated by
569 hyperglycemia and may be decreased with good metabolic control. It is essential for patients
570 with diabetes or history of gestational diabetes to maintain good metabolic control before
571 conception and throughout pregnancy. Careful monitoring of glucose control is essential in such
572 patients. Most experts recommend that insulin monotherapy be used during pregnancy to
573 maintain blood glucose levels as close to normal as possible. AVANDARYL should be used
574 during pregnancy only if the potential benefit justifies the potential risk to the fetus.

575 Human Data: There are no adequate and well-controlled trials with AVANDARYL or
576 its individual components in pregnant women. Rosiglitazone has been reported to cross the
577 human placenta and be detectable in fetal tissue. The clinical significance of these findings is
578 unknown.

579 Animal Studies: No animal studies have been conducted with AVANDARYL. The
580 following data are based on findings in studies performed with rosiglitazone or glimepiride
581 individually.

582 Rosiglitazone: There was no effect on implantation or the embryo with rosiglitazone
583 treatment during early pregnancy in rats, but treatment during mid-late gestation was associated
584 with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed
585 at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human
586 AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused
587 placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation
588 reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible
589 after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was
590 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately
591 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced
592 the number of uterine implantations and live offspring when juvenile female rats were treated at
593 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human
594 AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day

595 (approximately 4 times human AUC at the maximum recommended daily dose). There was no
596 effect on pre- or post-natal survival or growth.

597 **Glimepiride:** Glimepiride did not produce teratogenic effects in rats exposed orally up
598 to 4,000 mg/kg body weight (approximately 4,000 times the maximum recommended human
599 dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately
600 60 times the maximum recommended human dose based on surface area). Glimepiride has been
601 shown to be associated with intrauterine fetal death in rats when given in doses as low as
602 50 times the human dose based on surface area and in rabbits when given in doses as low as
603 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses
604 inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is
605 believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

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

614 **8.2 Labor and Delivery**

615 The effect of AVANDARYL or its components on labor and delivery in humans is
616 unknown.

617 **8.3 Nursing Mothers**

618 No trials have been conducted with AVANDARYL. It is not known whether
619 rosiglitazone or glimepiride is excreted in human milk. Because many drugs are excreted in
620 human milk, a decision should be made whether to discontinue nursing or to discontinue
621 AVANDARYL, taking into account the importance of the drug to the mother.

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

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

627 **8.4 Pediatric Use**

628 Safety and effectiveness of AVANDARYL in pediatric patients have not been
629 established. AVANDARYL and its components, rosiglitazone and glimepiride, are not indicated
630 for use in pediatric patients.

631 **8.5 Geriatric Use**

632 **Rosiglitazone:** Results of the population pharmacokinetic analysis showed that age does
633 not significantly affect the pharmacokinetics of rosiglitazone [see *Clinical Pharmacology*
634 (12.3)]. Therefore, no dosage adjustments are required for the elderly. In controlled clinical

635 trials, no overall differences in safety and effectiveness between older (≥ 65 years) and younger
636 (< 65 years) patients were observed.

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

640 Comparison of glimepiride pharmacokinetics in type 2 diabetes patients ≤ 65 years
641 ($N = 49$) and those > 65 years ($N = 42$) was performed in a trial using a dosing regimen of 6 mg
642 daily. There were no significant differences in glimepiride pharmacokinetics between the 2 age-
643 groups [see *Clinical Pharmacology (12.3)*].

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

648 Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering
649 drugs. In elderly, debilitated, or malnourished patients, or in patients with renal, hepatic or
650 adrenal insufficiency, the starting dose, dose increments, and maintenance dosage should be
651 conservative based upon blood glucose levels prior to and after initiation of treatment to avoid
652 hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly and in people
653 who are taking beta-adrenergic blocking drugs or other sympatholytic agents [see *Dosage and*
654 *Administration (2.4)*, *Warnings and Precautions (5.4)*, *Clinical Pharmacology (12.3)*].

655 **10 OVERDOSAGE**

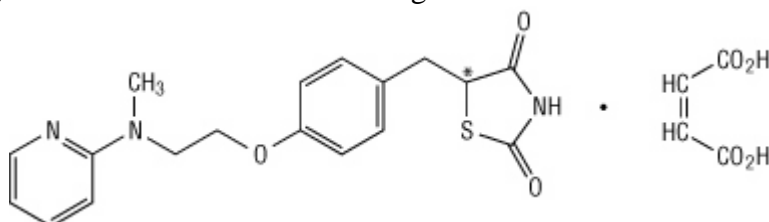
656 **Rosiglitazone:** Limited data are available with regard to overdose in humans. In
657 clinical trials in volunteers, rosiglitazone has been administered at single oral doses of up to
658 20 mg and was well tolerated. In the event of an overdose, appropriate supportive treatment
659 should be initiated as dictated by the patient's clinical status.

660 **Glimepiride:** Overdosage of sulfonylureas, including glimepiride, can produce
661 hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic
662 findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or
663 meal patterns. Close monitoring should continue until the physician is assured that the patient is
664 out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological
665 impairment occur infrequently, but constitute medical emergencies requiring immediate
666 hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a
667 rapid IV injection of concentrated (50%) glucose solution. This should be followed by a
668 continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood
669 glucose level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to
670 48 hours, because hypoglycemia may recur after apparent clinical recovery.

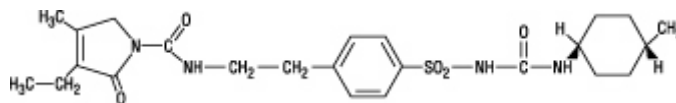
671 **11 DESCRIPTION**

672 AVANDARYL contains 2 oral antidiabetic drugs used in the management of type 2
673 diabetes: rosiglitazone maleate and glimepiride.

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



685
686 Glimepiride is an oral antidiabetic drug of the sulfonylurea class. Glimepiride is a white
687 to yellowish-white, crystalline, odorless to practically odorless powder. Chemically, glimepiride
688 is 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-
689 4-methylcyclohexyl)urea with a molecular weight of 490.62. The molecular formula for
690 glimepiride is $C_{24}H_{34}N_4O_5S$. Glimepiride is practically insoluble in water. The structural formula
691 of glimepiride is:



692
693 AVANDARYL is available for oral administration as tablets containing rosiglitazone
694 maleate and glimepiride, respectively, in the following strengths (expressed as rosiglitazone
695 maleate/glimepiride): 4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg, 8 mg/2 mg, and 8 mg/4 mg. Each
696 tablet contains the following inactive ingredients: hypromellose 2910, lactose monohydrate,
697 macrogol (polyethylene glycol), magnesium stearate, microcrystalline cellulose, sodium starch
698 glycolate, titanium dioxide, and 1 or more of the following: yellow, red, or black iron oxides.

699 12 CLINICAL PHARMACOLOGY

700 12.1 Mechanism of Action

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

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

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

719 In animal models, the antidiabetic activity of rosiglitazone was shown to be mediated by
720 increased sensitivity to insulin's action in the liver, muscle, and adipose tissues. Pharmacologic
721 studies in animal models indicate that rosiglitazone improves sensitivity to insulin in muscle and
722 adipose tissue and inhibits hepatic gluconeogenesis. The expression of the insulin-regulated
723 glucose transporter GLUT-4 was increased in adipose tissue. Rosiglitazone did not induce
724 hypoglycemia in animal models of type 2 diabetes and/or impaired glucose tolerance.

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

735 **12.2 Pharmacodynamics**

736 The lipid profiles of rosiglitazone and glimepiride in a clinical trial of patients with
737 inadequate glycemic control on diet and exercise were consistent with the known profile of each
738 monotherapy. AVANDARYL was associated with increases in HDL and LDL (3% to 4% for
739 each) and decreases in triglycerides (-4%), that were not considered to be clinically meaningful.

740 The pattern of LDL and HDL changes following therapy with rosiglitazone in patients
741 previously treated with a sulfonylurea was generally similar to those seen with rosiglitazone in
742 monotherapy. Rosiglitazone as monotherapy was associated with increases in total cholesterol,
743 LDL, and HDL and decreases in free fatty acids. The changes in triglycerides during therapy
744 with rosiglitazone were variable and were generally not statistically different from placebo or
745 glyburide controls.

746 **12.3 Pharmacokinetics**

747 In a bioequivalence trial of AVANDARYL 4 mg/4 mg, the area under the curve (AUC)
 748 and maximum concentration (C_{max}) of rosiglitazone following a single dose of the combination
 749 tablet were bioequivalent to rosiglitazone 4 mg concomitantly administered with glimepiride
 750 4 mg under fasted conditions. The AUC of glimepiride following a single fasted 4 mg/4 mg dose
 751 was equivalent to glimepiride concomitantly administered with rosiglitazone, while the C_{max} was
 752 13% lower when administered as the combination tablet (see Table 6).

753
 754 **Table 6. Pharmacokinetic Parameters for Rosiglitazone and Glimepiride (N = 28)**

| Parameter (Units) | Rosiglitazone | | Glimepiride | |
|----------------------------|----------------------|----------------------|----------------------|----------------------|
| | Regimen A | Regimen B | Regimen A | Regimen B |
| AUC_{0-inf} (ng.h/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.h/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) |
| $T_{1/2}$ (h) | 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} (h) | 1.00 (0.48-3.02) | 0.98 (0.48-5.97) | 3.02 (1.50-8.00) | 2.53 (1.00-8.03) |

755 AUC = area under the curve; C_{max} = maximum concentration; $T_{1/2}$ = terminal half-life;
 756 T_{max} = time of maximum concentration.

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

759 Data presented as geometric mean (range), except $T_{1/2}$ which is presented as arithmetic mean
 760 (range) and T_{max} , which is presented as median (range).

761
 762 The rate and extent of absorption of both the rosiglitazone component and glimepiride
 763 component of AVANDARYL when taken with food were equivalent to the rate and extent of
 764 absorption of rosiglitazone and glimepiride when administered concomitantly as separate tablets
 765 with food.

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

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

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

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

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

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

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

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

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

812 **Gender: Rosiglitazone:** Results of the population pharmacokinetics analysis showed
813 that the mean oral clearance of rosiglitazone in female patients (N = 405) was approximately 6%
814 lower compared with male patients of the same body weight (N = 642). Combination therapy
815 with rosiglitazone and sulfonylureas improved glycemic control in both males and females with
816 a greater therapeutic response observed in females. For a given body mass index (BMI), females
817 tend to have a greater fat mass than males. Since the molecular target of rosiglitazone, PPAR γ , is
818 expressed in adipose tissues, this differentiating characteristic may account, at least in part, for
819 the greater response to rosiglitazone in combination with sulfonylureas in females. Since therapy
820 should be individualized, no dose adjustments are necessary based on gender alone.

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

823 **Geriatric: Rosiglitazone:** Results of the population pharmacokinetics analysis
824 (N = 716 <65 years; N = 331 \geq 65 years) showed that age does not significantly affect the
825 pharmacokinetics of rosiglitazone.

826 **Glimepiride:** Comparison of glimepiride pharmacokinetics in type 2 diabetes
827 patients 65 years and younger with those older than 65 years was performed in a trial using a
828 dosing regimen of 6 mg daily. There were no significant differences in glimepiride
829 pharmacokinetics between the 2 age groups. The mean AUC at steady state for the older patients
830 was about 13% lower than that for the younger patients; the mean weight-adjusted clearance for
831 the older patients was about 11% higher than that for the younger patients. [*See Use in Specific*
832 *Populations (8.5).*]

833 **Hepatic Impairment:** Therapy with AVANDARYL should not be initiated if the
834 patient exhibits clinical evidence of active liver disease or increased serum transaminase levels
835 (ALT >2.5X upper limit of normal) at baseline [*see Warnings and Precautions (5.7)*].

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

841 **Glimepiride:** No trials of glimepiride have been conducted in patients with hepatic
842 insufficiency.

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

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

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

853 *Glimepiride:* A single-dose glimepiride, open-label trial was conducted in 15
854 patients with renal impairment. Glimepiride (3 mg) was administered to 3 groups of patients with
855 different levels of mean creatinine clearance (CL_{cr}); (Group I, $CL_{cr} = 77.7$ mL/min, N = 5),
856 (Group II, $CL_{cr} = 27.7$ mL/min, N = 3), and (Group III, $CL_{cr} = 9.4$ mL/min, N = 7). Glimepiride
857 was found to be well tolerated in all 3 groups. The results showed that glimepiride serum levels
858 decreased as renal function decreased. However, M1 and M2 serum levels (mean AUC values)
859 increased 2.3 and 8.6 times from Group I to Group III. The apparent terminal half-life ($t_{1/2}$) for
860 glimepiride did not change, while the half-lives for M1 and M2 increased as renal function
861 decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased
862 (44.4%, 21.9%, and 9.3% for Groups I to III). A multiple-dose titration trial was also conducted
863 in 16 type 2 diabetes patients with renal impairment using doses ranging from 1 to 8 mg daily for
864 3 months. The results were consistent with those observed after single doses. All patients with a
865 CL_{cr} less than 22 mL/min had adequate control of their glucose levels with a dosage regimen of
866 only 1 mg daily. The results from this trial suggest that a starting dose of 1 mg glimepiride, as
867 contained in AVANDARYL 4 mg/1 mg, may be given to type 2 diabetes patients with kidney
868 disease, and the dose may be titrated based on fasting glucose levels.

869 *Pediatric:* No pharmacokinetic data from trials in pediatric subjects are available for
870 AVANDARYL.

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

877 *Glimepiride:* The pharmacokinetics of glimepiride (1 mg) were evaluated in a
878 single-dose trial conducted in 30 type 2 diabetic patients (male = 7; female = 23) between ages
879 10 and 17 years. The mean AUC_{0-last} (338.8 ± 203.1 ng.h/mL), C_{max} (102.4 ± 47.7 ng/mL), and $t_{1/2}$
880 (3.1 ± 1.7 hours) were comparable to those previously reported in adults (AUC_{0-last}
881 315.2 ± 95.9 ng.h/mL, C_{max} 103.2 ± 34.3 ng/mL, and $t_{1/2}$ 5.3 ± 4.1 hours).

882 **12.4 Drug-drug Interactions**

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

887 Rosiglitazone: *Drugs That Inhibit, Induce, or are Metabolized by Cytochrome*
888 *P450:* In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the
889 major P450 enzymes at clinically relevant concentrations. In vitro data demonstrate that

890 rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9. [See Drug
891 Interactions (7.1).]

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

895 **Gemfibrozil:** Concomitant administration of gemfibrozil (600 mg twice daily), an
896 inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone
897 AUC by 127%, compared with the administration of rosiglitazone (4 mg once daily) alone.
898 Given the potential for dose-related adverse events with rosiglitazone, a decrease in the dose of
899 rosiglitazone may be needed when gemfibrozil is introduced [see Drug Interactions (7.1)].

900 **Rifampin:** Rifampin administration (600 mg once a day), an inducer of CYP2C8, for
901 6 days is reported to decrease rosiglitazone AUC by 66%, compared with the administration of
902 rosiglitazone (8 mg) alone [see Drug Interactions (7.1)].¹

903 **Glyburide:** Rosiglitazone (2 mg twice daily) taken concomitantly with glyburide (3.75
904 to 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose
905 concentrations in diabetic patients stabilized on glyburide therapy. Repeat doses of rosiglitazone
906 (8 mg once daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide
907 AUC and C_{max} of approximately 30%. In Japanese subjects, glyburide AUC and C_{max} slightly
908 increased following coadministration of rosiglitazone.

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

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

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

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

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

928 **Drugs Metabolized by Cytochrome P450:** A potential interaction between oral
929 miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported.

930 Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is
931 not known. There is a potential interaction of glimepiride with inhibitors (e.g., fluconazole) and
932 inducers (e.g., rifampicin) of cytochrome P450 2C9.

933 *Aspirin:* Coadministration of aspirin (1 g three times daily) and glimepiride led to a
934 34% decrease in the mean glimepiride AUC and, therefore, a 34% increase in the mean CL/F.
935 The mean C_{max} had a decrease of 4%. Blood glucose and serum C-peptide concentrations were
936 unaffected and no hypoglycemic symptoms were reported.

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

941 *Beta-Blockers:* Concomitant administration of propranolol (40 mg three times daily)
942 and glimepiride significantly increased C_{max} , AUC, and $t_{1/2}$ of glimepiride by 23%, 22%, and
943 15%, respectively, and it decreased CL/F by 18%. The recovery of M1 and M2 from urine,
944 however, did not change. The pharmacodynamic responses to glimepiride were nearly identical
945 in normal subjects receiving propranolol and placebo. Pooled data from clinical trials in patients
946 with type 2 diabetes showed no evidence of clinically significant adverse interactions with
947 uncontrolled concurrent administration of beta-blockers. However, if beta-blockers are used,
948 caution should be exercised and patients should be warned about the potential for hypoglycemia.

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

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

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

965 **13 NONCLINICAL TOXICOLOGY**

966 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

967 No animal studies have been conducted with AVANDARYL. The following data are
968 based on findings in studies performed with rosiglitazone or glimepiride alone.

969 Rosiglitazone: Carcinogenesis: A 2-year carcinogenicity study was conducted in
970 Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose
971 equivalent to approximately 12 times human AUC at the maximum recommended human daily
972 dose). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05 mg/kg/day,
973 0.3 mg/kg/day, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times
974 human AUC at the maximum recommended human daily dose for male and female rats,
975 respectively).

976 Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of
977 adipose hyperplasia in the mouse at doses ≥ 1.5 mg/kg/day (approximately 2 times human AUC
978 at the maximum recommended human daily dose). In rats, there was a significant increase in the
979 incidence of benign adipose tissue tumors (lipomas) at doses ≥ 0.3 mg/kg/day (approximately
980 2 times human AUC at the maximum recommended human daily dose). These proliferative
981 changes in both species are considered due to the persistent pharmacological overstimulation of
982 adipose tissue.

983 Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial
984 assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in
985 vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about
986 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic
987 activation.

988 Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats
989 given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended
990 human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility
991 (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and
992 estradiol (approximately 20 and 200 times human AUC at the maximum recommended human
993 daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times
994 human AUC at the maximum recommended human daily dose). In juvenile rats dosed from
995 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male
996 reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in
997 females (approximately 68 times human AUC at the maximum recommended daily dose). In
998 monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at
999 the maximum recommended human daily dose, respectively) diminished the follicular phase rise
1000 in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal
1001 phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct
1002 inhibition of ovarian steroidogenesis.

1003 Glimepiride: Carcinogenesis: Studies in rats at doses of up to 5,000 parts per million
1004 (ppm) in complete feed (approximately 340 times the maximum recommended human dose,
1005 based on surface area) for 30 months showed no evidence of carcinogenesis. In mice,
1006 administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma
1007 formation which was dose-related and is thought to be the result of chronic pancreatic
1008 stimulation. The no-effect dose for adenoma formation in mice in this study was 320 ppm in

1009 complete feed, or 46 to 54 mg/kg body weight/day. This is about 35 times the maximum human
1010 recommended dose based on surface area.

1011 *Mutagenesis:* Glimepiride was non-mutagenic in a battery of in vitro and in vivo
1012 mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled
1013 DNA synthesis, mouse micronucleus test).

1014 *Impairment of Fertility:* There was no effect of glimepiride on male mouse fertility in
1015 animals exposed up to 2,500 mg/kg body weight (>1,700 times the maximum recommended
1016 human dose based on surface area). Glimepiride had no effect on the fertility of male and female
1017 rats administered up to 4,000 mg/kg body weight (approximately 4,000 times the maximum
1018 recommended human dose based on surface area).

1019 **13.2 Animal Toxicology and/or Pharmacology**

1020 Rosiglitazone: Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day),
1021 and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human
1022 AUC at the maximum recommended human daily dose, respectively). Effects in juvenile rats
1023 were consistent with those seen in adults. Morphometric measurement indicated that there was
1024 hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result
1025 of plasma volume expansion.

1026 Glimepiride: Reduced serum glucose values and degranulation of the pancreatic beta
1027 cells were observed in beagle dogs exposed to glimepiride 320 mg/kg/day for 12 months
1028 (approximately 1,000 times the recommended human dose based on surface area). No evidence
1029 of tumor formation was observed in any organ. One female and one male dog developed bilateral
1030 subcapsular cataracts. Non-GLP studies indicated that glimepiride was unlikely to exacerbate
1031 cataract formation. Evaluation of the co-cataractogenic potential of glimepiride in several
1032 diabetic and cataract rat models was negative and there was no adverse effect of glimepiride on
1033 bovine ocular lens metabolism in organ culture [*see Adverse Reactions (6.1)*].

1034 **14 CLINICAL STUDIES**

1035 **14.1 Patients Inadequately Controlled on Diet and Exercise**

1036 In a 28-week, randomized, double-blind, clinical trial, 901 patients with type 2 diabetes
1037 inadequately controlled on diet and exercise alone (baseline mean fasting plasma glucose [FPG]
1038 211 mg/dL and baseline mean HbA1c 9.1%) were started on AVANDARYL 4 mg/1 mg,
1039 rosiglitazone 4 mg, or glimepiride 1 mg. Doses could be increased at 4-week intervals to reach a
1040 target mean daily glucose of ≤ 110 mg/dL. Patients who received AVANDARYL were
1041 randomized to 1 of 2 titration schemes differing in the maximum total daily dose (4 mg/4 mg or
1042 8 mg/4 mg). The maximum total daily dose was 8 mg for rosiglitazone monotherapy and 4 mg
1043 for glimepiride monotherapy. All treatments were administered as a once-daily regimen.
1044 Improvements in FPG and HbA1c were observed in patients treated with AVANDARYL
1045 compared with either rosiglitazone or glimepiride alone (see Table 7).
1046

1047 **Table 7. Glycemic Parameters in a 28-Week Trial of AVANDARYL in Patients With Type**
 1048 **2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise**

| Parameter | 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 ^a | -37 ^a |
| – AVANDARYL and rosiglitazone | — | — | -16 ^a | -23 ^a |
| % 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 ^a | -0.7 ^a |
| – AVANDARYL and rosiglitazone | — | — | -0.7 ^a | -0.8 ^a |
| % of patients with ≥0.7% decrease from baseline | 82% | 76% | 93% | 93% |
| % of patients at HbA1c Target <7.0% ^b | 49% | 46% | 75% | 72% |

1049 ^a Least squared means, $P < 0.0001$ compared with monotherapy.

1050 ^b Response is related to baseline HbA1c.

1051
 1052 Treatment with AVANDARYL resulted in statistically significant improvements in FPG
 1053 and HbA1c compared with each of the monotherapies. However, when considering choice of
 1054 therapy for drug-naïve patients, the risk-benefit of initiating monotherapy or dual therapy should
 1055 be considered. In particular, the risk of hypoglycemia and weight gain with dual therapy should
 1056 be taken into account. [See Warnings and Precautions (5.4, 5.6), Adverse Reactions (6.1).]

1057 **14.2 Patients Previously Treated With Sulfonylureas**

1058 The safety and efficacy of rosiglitazone added to a sulfonylurea have been studied in
1059 clinical trials in patients with type 2 diabetes inadequately controlled on sulfonylureas alone. No
1060 clinical trials have been conducted with the fixed-dose combination of AVANDARYL in
1061 patients inadequately controlled on a sulfonylurea or who have initially responded to
1062 rosiglitazone alone and require additional glycemic control.

1063 A total of 3,457 patients with type 2 diabetes participated in ten 24- to 26-week
1064 randomized, double-blind, placebo/active-controlled trials and one 2-year double-blind, active-
1065 controlled trial in elderly patients designed to assess the efficacy and safety of rosiglitazone in
1066 combination with a sulfonylurea. Rosiglitazone 2 mg, 4 mg, or 8 mg daily, was administered
1067 either once daily (3 trials) or in divided doses twice daily (7 trials), to patients inadequately
1068 controlled on a submaximal or maximal dose of sulfonylurea.

1069 In these trials, the combination of rosiglitazone 4 mg or 8 mg daily (administered as
1070 single- or twice-daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c
1071 compared with placebo plus sulfonylurea or further up-titration of the sulfonylurea. Table 8
1072 shows pooled data for 8 trials in which rosiglitazone added to sulfonylurea was compared with
1073 placebo plus sulfonylurea.

1074

1075 **Table 8. Glycemic Parameters in 24- to 26-Week Combination Trials of Rosiglitazone Plus**
 1076 **Sulfonylurea**

| Twice-Daily Divided Dosing (5 Trials) | 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 ^a | — | -53 ^a |
| % 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 ^a | — | -1.4 ^a |
| % of patients with ≥0.7% decrease from baseline | 21% | 60% | 23% | 75% |
| Once-Daily Dosing (3 Trials) | 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 ^a | — | -66 ^a |
| % 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 (mean) | 0.4 | -0.5 | 0.1 | -1.2 |
| Difference from sulfonylurea alone (adjusted mean) | - | -0.9 ^a | - | -1.4 ^a |
| % of patients with ≥0.7% decrease from baseline | 11% | 36% | 20% | 68% |

1077 ^a *P* <0.0001 compared with sulfonylurea alone.

1078
 1079 One of the 24- to 26-week trials included patients who were inadequately controlled on
 1080 maximal doses of glyburide and switched to 4 mg of rosiglitazone daily as monotherapy; in this
 1081 group, loss of glycemic control was demonstrated, as evidenced by increases in FPG and HbA1c.

1082 In a 2-year double-blind trial, elderly patients (aged 59 to 89 years) on half-maximal
1083 sulfonylurea (glipizide 10 mg twice daily) were randomized to the addition of rosiglitazone
1084 (N = 115, 4 mg once daily to 8 mg as needed) or to continued up-titration of glipizide (N = 110),
1085 to a maximum of 20 mg twice daily. Mean baseline FPG and HbA1c were 157 mg/dL and
1086 7.72%, respectively, for the rosiglitazone plus glipizide arm and 159 mg/dL and 7.65%,
1087 respectively, for the glipizide up-titration arm. Loss of glycemic control (FPG \geq 180 mg/dL)
1088 occurred in a significantly lower proportion of patients (2%) on rosiglitazone plus glipizide
1089 compared with patients in the glipizide up-titration arm (28.7%). About 78% of the patients on
1090 combination therapy completed the 2 years of therapy while only 51% completed on glipizide
1091 monotherapy. The effect of combination therapy on FPG and HbA1c was durable over the 2-year
1092 trial period, with patients achieving a mean of 132 mg/dL for FPG and a mean of 6.98% for
1093 HbA1c compared with no change on the glipizide arm.

1094 **15 REFERENCES**

1095 1. Park JY, Kim KA, Kang MH, et al. Effect of rifampin on the pharmacokinetics of
1096 rosiglitazone in healthy subjects. *Clin Pharmacol Ther* 2004;75:157-162.

1097 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1098 Each rounded triangular tablet contains rosiglitazone as the maleate and glimepiride as
1099 follows:

1100 4 mg/1 mg – yellow, gsk debossed on one side and 4/1 on the other.

1101 4 mg/2 mg – orange, gsk debossed on one side and 4/2 on the other.

1102 4 mg/4 mg – pink, gsk debossed on one side and 4/4 on the other.

1103 8 mg/2 mg – pale pink, gsk debossed on one side and 8/2 on the other.

1104 8 mg/4 mg – red, gsk debossed on one side and 8/4 on the other.

1105

1106 4 mg/1 mg bottles of 30: NDC 0173-0841-13

1107 4 mg/2 mg bottles of 30: NDC 0173-0842-13

1108 4 mg/4 mg bottles of 30: NDC 0173-0843-13

1109 8 mg/2 mg bottles of 30: NDC 0173-0844-13

1110 8 mg/4 mg bottles of 30: NDC 0173-0845-13

1111

1112 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Dispense in a
1113 tight, light-resistant container.

1114 **17 PATIENT COUNSELING INFORMATION**

1115 *Advise the patient to read the FDA-approved patient labeling (Medication Guide).*

1116 There are multiple medications available to treat type 2 diabetes. The benefits and risks
1117 of each available diabetes medication should be taken into account when choosing a particular
1118 diabetes medication for a given patient.

1119 Patients should be informed of the following:

- 1120 • AVANDARYL is not recommended in patients with symptomatic heart failure.
- 1121 • A meta-analysis of mostly short-term trials suggested an increased risk for myocardial
- 1122 infarction with rosiglitazone compared with placebo. Data from long-term clinical trials of
- 1123 rosiglitazone versus other antidiabetes agents (metformin or sulfonylureas), including a
- 1124 cardiovascular outcome trial (RECORD), observed no difference in overall mortality or in
- 1125 major adverse cardiovascular events (MACE) and its components.
- 1126 • AVANDARYL is not recommended for patients who are taking insulin.
- 1127 • Management of type 2 diabetes should include diet control. Caloric restriction, weight loss,
- 1128 and exercise are essential for the proper treatment of the diabetic patient because they help
- 1129 improve insulin sensitivity. This is important not only in the primary treatment of type 2
- 1130 diabetes, but also in maintaining the efficacy of drug therapy.
- 1131 • It is important to adhere to dietary instructions and to regularly have blood glucose and
- 1132 glycosylated hemoglobin (HbA1c) tested. It can take 2 weeks to see a reduction in blood
- 1133 glucose and 2 to 3 months to see the full effect of AVANDARYL.
- 1134 • The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its
- 1135 development should be explained to patients and their family members.
- 1136 • Blood will be drawn to check their liver function prior to the start of therapy and periodically
- 1137 thereafter per the clinical judgment of the healthcare professional. Patients with unexplained
- 1138 symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should
- 1139 immediately report these symptoms to their physician.
- 1140 • Patients who experience an unusually rapid increase in weight or edema or who develop
- 1141 shortness of breath or other symptoms of heart failure while on AVANDARYL should
- 1142 immediately report these symptoms to their physician.
- 1143 • AVANDARYL should be taken with the first meal of the day.
- 1144 • Therapy with rosiglitazone, like other thiazolidinediones, may result in ovulation in some
- 1145 premenopausal anovulatory women. As a result, these patients may be at an increased risk for
- 1146 pregnancy while taking AVANDARYL. Thus, adequate contraception in premenopausal
- 1147 women should be recommended. This possible effect has not been specifically investigated
- 1148 in clinical trials so the frequency of this occurrence is not known.

1149
1150 AVANDARYL is a registered trademark of the GSK group of companies.
1151



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1154 Research Triangle Park, NC 27709
1155
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MEDICATION GUIDE

AVANDARYL® (ah-VAN-duh-riil)

(rosiglitazone maleate and glimepiride) tablets

Read this Medication Guide carefully before you start taking AVANDARYL 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 the most important information I should know about AVANDARYL?

AVANDARYL may cause serious side effects, including:

New or worse heart failure

- The risk of heart failure may be higher in people who take AVANDARYL with insulin. Most people who take insulin should not also take AVANDARYL.
- Rosiglitazone, one of the two drugs that make up AVANDARYL, can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Heart failure means your heart does not pump blood well enough.
- If you have severe heart failure, you cannot start AVANDARYL.
- If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, AVANDARYL may not be right for you.

Call your doctor right away if you have any of the following:

- swelling or fluid retention, especially in the ankles or legs
- shortness of breath or trouble breathing, especially when you lie down
- an unusually fast increase in weight
- unusual tiredness

AVANDARYL can have other serious side effects. Be sure to read the section “What are possible side effects of AVANDARYL?”

What is AVANDARYL?

AVANDARYL contains 2 prescription medicines to treat diabetes, rosiglitazone maleate (AVANDIA®) and glimepiride. AVANDARYL is used with diet and exercise to treat adults with 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 and does not cause

1194 your body to make more insulin. These medicines can work together to help control
1195 your blood sugar.

1196 AVANDARYL is not for people with type 1 diabetes mellitus or to treat a condition
1197 called diabetic ketoacidosis.

1198 It is not known if AVANDARYL is safe and effective in children younger than
1199 18 years old.

1200 **Who should not take AVANDARYL?**

1201 Many people with heart failure should not start taking AVANDARYL. See “What
1202 should I tell my doctor before taking AVANDARYL?”

1203 **Do not** take AVANDARYL if you are allergic to rosiglitazone or any of the
1204 ingredients in AVANDARYL. See the end of this leaflet for a complete list of
1205 ingredients in AVANDARYL.

1206 Symptoms of a severe allergic reaction with AVANDARYL may include:

- 1207 • swelling of your face, lips, tongue, or throat
- 1208 • problems with breathing or swallowing
- 1209 • skin rash or itching
- 1210 • raised red areas on your skin (hives)
- 1211 • blisters on your skin or in your mouth, nose, or eyes
- 1212 • peeling of your skin
- 1213 • fainting or feeling dizzy
- 1214 • very rapid heartbeat

1215 **What should I tell my doctor before taking AVANDARYL?**

1216 Before starting AVANDARYL, ask your doctor about what the choices are for
1217 diabetes medicines and what the expected benefits and possible risks are for you in
1218 particular.

1219 Before taking AVANDARYL, tell your doctor about all of your medical conditions,
1220 including if you:

- 1221 • **have heart problems or heart failure.**
- 1222 • **have type 1 (“juvenile”) diabetes or had diabetic ketoacidosis.** These
1223 conditions should be treated with insulin and should not be treated with
1224 AVANDARYL.
- 1225 • **have a type of diabetic eye disease called macular edema** (swelling of the
1226 back of the eye).
- 1227 • **have liver problems.** Your doctor should do blood tests to check your liver
1228 before you start taking AVANDARYL and during treatment as needed.

- 1229 • **had liver problems while taking REZULIN™ (troglitazone), another**
1230 **medicine for diabetes.**
- 1231 • **have kidney problems.** If people with kidney problems use AVANDARYL, they
1232 may need a lower dose of the medication.
- 1233 • **have glucose 6-phosphate dehydrogenase (G6PD) deficiency.** This
1234 condition runs in families. People with G6PD deficiency who take glimepiride
1235 (one of the medicines in AVANDARYL) may develop hemolytic anemia (fast
1236 breakdown of red blood cells).
- 1237 • **are pregnant or plan to become pregnant.** It is not known if AVANDARYL
1238 can harm your unborn baby. You and your doctor should talk about the best way
1239 to control your diabetes during pregnancy. If you are a premenopausal woman
1240 (before the “change of life”) who does not have regular monthly periods,
1241 AVANDARYL may increase your chances of becoming pregnant. Talk to your
1242 doctor about birth control choices while taking AVANDARYL. Tell your doctor
1243 right away if you become pregnant while taking AVANDARYL.
- 1244 • **are breastfeeding or planning to breastfeed.** It is not known if AVANDARYL
1245 passes into breast milk. You and your doctor should decide if you will take
1246 AVANDARYL or breastfeed. You should not do both.

1247 Tell your doctor about all of the medicines you take including prescription and non-
1248 prescription medicines, vitamins or herbal supplements. AVANDARYL and certain
1249 other medicines can affect each other and may lead to serious side effects including
1250 high or low blood sugar, or heart problems. Especially tell your doctor if you take:

- 1251 • **insulin.**
- 1252 • **any medicines for high blood pressure, high cholesterol or heart failure,**
1253 **or for prevention of heart disease or stroke.**

1254 Know the medicines you take. Keep a list of all your medicines and show it to your
1255 doctor and pharmacist before you start a new medicine. They will tell you if it is
1256 alright to take AVANDARYL with other medicines.

1257 **How should I take AVANDARYL?**

- 1258 • Take AVANDARYL exactly as prescribed. Your doctor may need to change your
1259 dose until your blood sugar is better controlled.
- 1260 • Take AVANDARYL by mouth one time each day with your first main meal.
- 1261 • It usually takes a few days for AVANDARYL to start lowering your blood sugar. It
1262 may take 2 to 3 months to see the full effect on your blood sugar level.
- 1263 • If you miss a dose of AVANDARYL, take it as soon as you remember unless it is
1264 time to take your next dose. Take your next dose at the usual time. Do not take
1265 double doses to make up for a missed dose.
- 1266 • If you take too much AVANDARYL, call your doctor or poison control center right
1267 away.

- 1268 • Test your blood sugar regularly as your doctor tells you.
1269 • Your doctor should do blood tests to check your liver before you start
1270 AVANDARYL and during treatment as needed. Your doctor should also do regular
1271 blood sugar tests (for example, "A1c") to monitor your response to AVANDARYL.
1272 • Call your doctor if you get sick, get injured, get an infection, or have surgery.
1273 AVANDARYL may not control your blood sugar levels during these times. Your
1274 doctor may need to stop AVANDARYL for a short time and give you insulin to
1275 control your blood sugar level.
1276 • Diet and exercise can help your body use its blood sugar better. It is important
1277 to stay on your recommended diet, lose extra weight, and get regular exercise
1278 while taking AVANDARYL.

1279 **What are possible side effects of AVANDARYL?**

1280 **AVANDARYL may cause serious side effects, including:**

- 1281 • **New or worse heart failure.** See "What is the most important information I
1282 should know about AVANDARYL?"
1283 • **Heart attack.** AVANDARYL may increase the risk of a heart attack. Talk to your
1284 doctor about what this means to you.

1285 **Symptoms of a heart attack can include the following:**

- 1286 • chest discomfort in the center of your chest that lasts for more than a few
1287 minutes, or that goes away or comes back
1288 • chest discomfort that feels like uncomfortable pressure, squeezing, fullness, or
1289 pain
1290 • pain or discomfort in your arms, back, neck, jaw, or stomach
1291 • shortness of breath with or without chest discomfort
1292 • breaking out in a cold sweat
1293 • nausea or vomiting
1294 • feeling lightheaded

1295 **Call your doctor or go to the nearest hospital emergency room right
1296 away if you think you are having a heart attack.**

- 1297 • **Swelling (edema).** AVANDARYL can cause swelling due to fluid retention. See
1298 "What is the most important information I should know about AVANDARYL?"
1299 • **Low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness, or
1300 hunger may mean that your blood sugar is too low. This can happen if you skip
1301 meals, drink alcohol, use another medicine that lowers blood sugar, exercise
1302 (particularly hard or long), or if you have certain medical problems. Call your
1303 doctor if low blood sugar levels are a problem for you.
1304 • **Weight gain.** Rosiglitazone, one of the medicines in AVANDARYL, can cause
1305 weight gain that may be due to fluid retention or extra body fat. Weight gain can

1306 be a serious problem for people with certain conditions including heart problems.
1307 See "What is the most important information I should know about AVANDARYL?"

- 1308 • **Liver problems.** It is important for your liver to be working normally when you
1309 take AVANDARYL. Your doctor should do blood tests to check your liver before
1310 you start taking AVANDARYL and during treatment as needed. Call your doctor
1311 right away if you have unexplained symptoms such as:
 - 1312 • nausea or vomiting
 - 1313 • stomach pain
 - 1314 • unusual or unexplained tiredness
 - 1315 • loss of appetite
 - 1316 • dark urine
 - 1317 • yellowing of your skin or the whites of your eyes
- 1318 • **Macular edema** (a diabetic eye disease with swelling in the back of the eye).
1319 Tell your doctor right away if you have any changes in your vision. Your doctor
1320 should check your eyes regularly. Very rarely, some people have had vision
1321 changes due to swelling in the back of the eye while taking rosiglitazone, one of
1322 the medicines in AVANDARYL.
- 1323 • **Fractures (broken bones)**, usually in the hand, upper arm, or foot. Talk to
1324 your doctor for advice on how to keep your bones healthy.
- 1325 • **Low red blood cell count (anemia).**
- 1326 • **Ovulation** (release of egg from an ovary in women) leading to pregnancy.
1327 Ovulation may happen in premenopausal women who do not have regular
1328 monthly periods. This can increase the chance of pregnancy. See "What should I
1329 tell my doctor before taking AVANDARYL?"

1330 The most common side effects with AVANDARYL include cold-like symptoms and
1331 headache.

1332 Call your doctor for medical advice about side effects. You may report side effects
1333 to FDA at 1-800-FDA-1088.

1334 **How should I store AVANDARYL?**

- 1335 • Store AVANDARYL at room temperature, 59°F to 86°F (15°C to 30°C). Keep
1336 AVANDARYL in the container it comes in. Keep the container closed tightly.
- 1337 • Safely, throw away AVANDARYL that is out of date or no longer needed.

1338 Keep AVANDARYL and all medicines out of the reach of children.

1339 **General information about AVANDARYL**

1340 Medicines are sometimes prescribed for purposes other than those listed in a
1341 Medication Guide. Do not use AVANDARYL for a condition for which it was not

1342 prescribed. Do not give AVANDARYL to other people, even if they have the same
1343 symptoms you have. It may harm them.

1344 This Medication Guide summarizes important information about AVANDARYL. If you
1345 would like more information, talk with your doctor. You can ask your doctor or
1346 pharmacist for information about AVANDARYL that is written for healthcare
1347 professionals. You can also find out more about AVANDARYL by calling 1-888-825-
1348 5249.

1349 **What are the ingredients in AVANDARYL?**

1350 Active Ingredients: rosiglitazone maleate and glimepiride.

1351 Inactive Ingredients: hypromellose 2910, lactose monohydrate, macrogol
1352 (polyethylene glycol), magnesium stearate, microcrystalline cellulose, sodium
1353 starch glycolate, titanium dioxide, triacetin, and 1 or more of the following: yellow,
1354 red, or black iron oxides.

1355 Always check to make sure that the medicine you are taking is the correct one.

1356 AVANDARYL tablets are triangles with rounded corners and look like this:

1357 4 mg/1 mg – yellow with “gsk” on one side and “4/1” on the other.

1358 4 mg/2 mg – orange with “gsk” on one side and “4/2” on the other.

1359 4 mg/4 mg – pink with “gsk” on one side and “4/4” on the other.

1360 8 mg/2 mg – pale pink with “gsk” on one side and “8/2” on the other.

1361 8 mg/4 mg – red with “gsk” on one side and “8/4” on the other.

1362 AVANDARYL and AVANDIA are registered trademarks of the GSK group of
1363 companies.

1364 REZULIN is a trademark of its respective owner and is not a trademark of the GSK
1365 group of companies. The maker of this brand is not affiliated with and does not
1366 endorse the GSK group of companies or its products.

1367 **This Medication Guide has been approved by the U.S. Food and Drug**
1368 **Administration.**



1369

1370 GlaxoSmithKline

1371 Research Triangle Park, NC 27709

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1374 AVR: XMG