

## 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 AND MYOCARDIAL INFARCTION

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)

• A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with a statistically significant increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, showed a statistically non-significant increased risk of myocardial infarction and a statistically non-significant decreased risk of death. There have been no clinical trials directly comparing cardiovascular risk of rosiglitazone and ACTOS® (pioglitazone, another thiazolidinedione), but in a separate trial, pioglitazone (when compared to placebo) did not show an increased risk of myocardial infarction or death. (5.3)

• Because of the potential increased risk of myocardial infarction, AVANDARYL is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1-800-AVANDIA or visit [www.AVANDIA.com](http://www.AVANDIA.com). [See Warnings and Precautions (5.4).]

### RECENT MAJOR CHANGES

Boxed Warning	02/2011
Indications and Usage (1)	02/2011
Dosage and Administration (2)	02/2011
Warnings and Precautions, Cardiac Failure (5.2)	02/2011
Warnings and Precautions, Major Adverse Cardiovascular Events (5.3)	02/2011
Warnings and Precautions, Rosiglitazone REMS Program (5.4)	XX/2011
Warnings and Precautions, Fractures (5.10)	02/2011

### INDICATIONS AND USAGE

AVANDARYL is a combination antidiabetic product containing a thiazolidinedione and a sulfonylurea. After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of rosiglitazone, this drug is indicated as an adjunct to diet and exercise to improve glycemic control when treatment with both rosiglitazone and glimepiride is appropriate in adults with type 2 diabetes who either are:

- already taking rosiglitazone, or
- not already taking rosiglitazone and unable to achieve glycemic control on other diabetes medications and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS) or pioglitazone-containing products (ACTOPLUS MET®, ACTOPLUS MET XR®, DUETACT®) for

medical reasons. (1)

Other 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)

### 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)
- Increased risk of myocardial infarction has been observed in a meta-analysis of 52 clinical trials of rosiglitazone (incidence rate 0.4% versus 0.3%). (5.3)
- Use with insulin is not recommended. (1, 5.2, 5.3)
- Severe hypoglycemia may occur. Use particular care in elderly or debilitated patients and those with adrenal, pituitary, renal or hepatic insufficiency. (5.5)
- Dose-related edema (5.6), weight gain (5.7), and anemia (5.11) may occur.
- Macular edema has been reported. (5.9)
- Increased incidence of bone fracture. (5.10)
- The glimepiride component may cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Consider a non-sulfonylurea alternative in these patients. (5.12)

### ADVERSE REACTIONS

Common adverse reactions (≥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](http://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

- Do not use during pregnancy. No human or animal data. (8.1)
- Safety and effectiveness in children under 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: XX/2011

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\*Sections or subsections omitted from the full prescribing information are not listed.

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## 1 FULL PRESCRIBING INFORMATION

### 2 **WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION**

- 3 ● Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in  
4 some patients [*see Warnings and Precautions (5.2)*]. After initiation of AVANDARYL, and  
5 after dose increases, observe patients carefully for signs and symptoms of heart failure  
6 (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms  
7 develop, the heart failure should be managed according to current standards of care.  
8 Furthermore, discontinuation or dose reduction of AVANDARYL must be considered.
- 9 ● AVANDARYL is not recommended in patients with symptomatic heart failure. Initiation of  
10 AVANDARYL in patients with established NYHA Class III or IV heart failure is  
11 contraindicated. [*See Contraindications (4) and Warnings and Precautions (5.2).*]
- 12 ● A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of  
13 which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an  
14 increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067  
15 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or  
16 placebo, showed a statistically non-significant increased risk of myocardial infarction, and a  
17 statistically non-significant decreased risk of death. There have been no clinical trials directly  
18 comparing cardiovascular risk of rosiglitazone and ACTOS<sup>®</sup> (pioglitazone, another  
19 thiazolidinedione), but in a separate trial, pioglitazone (when compared to placebo) did not  
20 show an increased risk of myocardial infarction or death. [*See Warnings and Precautions*  
21 *(5.3).*]
- 22 ● Because of the potential increased risk of myocardial infarction, AVANDARYL is available  
23 only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines  
24 Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1-  
25 800-AVANDIA or visit [www.AVANDIA.com](http://www.AVANDIA.com). [*See Warnings and Precautions (5.4).*]

### 26 **1 INDICATIONS AND USAGE**

27 After consultation with a healthcare professional who has considered and advised the  
28 patient of the risks and benefits of rosiglitazone, AVANDARYL<sup>®</sup> is indicated as an adjunct to  
29 diet and exercise to improve glycemic control when treatment with both rosiglitazone and  
30 glimepiride is appropriate in adults with type 2 diabetes mellitus who either are:

- 31 ● already taking rosiglitazone, or
- 32 ● not already taking rosiglitazone and unable to achieve glycemic control on other diabetes  
33 medications and, in consultation with their healthcare provider, have decided not to take  
34 pioglitazone (ACTOS<sup>®</sup>) or pioglitazone-containing products (ACTOSPLUS MET<sup>®</sup>,  
35 ACTOPLUS MET XR<sup>®</sup>, DUETACT<sup>®</sup>) for medical reasons.

36 **Other Important Limitations of Use:**

- 37 • Due to its mechanism of action, rosiglitazone is active only in the presence of endogenous  
38 insulin. Therefore, AVANDARYL should not be used in patients with type 1 diabetes or for  
39 the treatment of diabetic ketoacidosis.  
40 • Coadministration of AVANDARYL with insulin is not recommended [see *Warnings and*  
41 *Precautions (5.2, 5.3)*].

42 **2 DOSAGE AND ADMINISTRATION**

43 Prior to prescribing AVANDARYL, refer to *Indications and Usage (1)* for appropriate  
44 patient selection. Only prescribers enrolled in the AVANDIA-Rosiglitazone Medicines Access  
45 Program can prescribe AVANDARYL [see *Warnings and Precautions (5.4)*].

46 **2.1 Starting Dose**

47 The recommended starting dose is 4 mg/1 mg administered once daily with the first meal  
48 of the day. For adults already treated with a sulfonylurea or rosiglitazone, a starting dose of  
49 4 mg/2 mg may be considered.

50 All patients should start the rosiglitazone component of AVANDARYL at the lowest  
51 recommended dose. Further increases in the dose of rosiglitazone should be accompanied by  
52 careful monitoring for adverse events related to fluid retention [see **Boxed Warning and**  
53 *Warnings and Precautions (5.6)*].

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

57 **2.2 Dose Titration**

58 Dose increases should be individualized according to the glycemic response of the  
59 patient. Patients who may be more sensitive to glimepiride [see *Warnings and Precautions*  
60 *(5.5)*], including the elderly, debilitated, or malnourished, and those with renal, hepatic, or  
61 adrenal insufficiency, should be carefully titrated to avoid hypoglycemia. If hypoglycemia  
62 occurs during up-titration of the dose or while maintained on therapy, a dosage reduction of the  
63 glimepiride component of AVANDARYL may be considered. Increases in the dose of  
64 rosiglitazone should be accompanied by careful monitoring for adverse events related to fluid  
65 retention [see **Boxed Warning and Warnings and Precautions (5.6)].**

66 **To switch to AVANDARYL for adults currently treated with rosiglitazone,** dose  
67 titration of the glimepiride component of AVANDARYL is recommended if patients are not  
68 adequately controlled after 1 to 2 weeks. The glimepiride component may be increased in no  
69 more than 2 mg increments. After an increase in the dosage of the glimepiride component, dose  
70 titration of AVANDARYL is recommended if patients are not adequately controlled after 1 to 2  
71 weeks.

72 **To switch to AVANDARYL for adults currently treated with sulfonylurea,** it may  
73 take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of the  
74 rosiglitazone component. Therefore, dose titration of the rosiglitazone component of

75 AVANDARYL is recommended if patients are not adequately controlled after 8 to 12 weeks.  
76 Patients should be observed carefully (1 to 2 weeks) for hypoglycemia when being transferred  
77 from longer half-life sulfonylureas (e.g., chlorpropamide) to AVANDARYL due to potential  
78 overlapping of drug effect. After an increase in the dosage of the rosiglitazone component, dose  
79 titration of AVANDARYL is recommended if patients are not adequately controlled after 2 to 3  
80 months.

### 81 **2.3 Maximum Dose**

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

### 83 **2.4 Specific Patient Populations**

84 Elderly and Malnourished Patients and Those With Renal, Hepatic, or Adrenal  
85 Insufficiency: In elderly, debilitated, or malnourished patients, or in patients with renal, hepatic,  
86 or adrenal insufficiency, the starting dose, dose increments, and maintenance dosage of  
87 AVANDARYL should be conservative to avoid hypoglycemic reactions. [See *Warnings and*  
88 *Precautions (5.5) and Clinical Pharmacology (12.3).*]

89 Hepatic Impairment: Liver enzymes should be measured prior to initiating treatment  
90 with AVANDARYL. Therapy with AVANDARYL should not be initiated if the patient exhibits  
91 clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X  
92 upper limit of normal at start of therapy). After initiation of AVANDARYL, liver enzymes  
93 should be monitored periodically per the clinical judgment of the healthcare professional. [See  
94 *Warnings and Precautions (5.8) and Clinical Pharmacology (12.3).*]

95 Pregnancy and Lactation: AVANDARYL should not be used during pregnancy or in  
96 nursing mothers.

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

## 100 **3 DOSAGE FORMS AND STRENGTHS**

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

- 102 • 4 mg/1 mg – yellow, gsk debossed on one side and 4/1 on the other.
- 103 • 4 mg/2 mg – orange, gsk debossed on one side and 4/2 on the other.
- 104 • 4 mg/4 mg – pink, gsk debossed on one side and 4/4 on the other.
- 105 • 8 mg/2 mg – pale pink, gsk debossed on one side and 8/2 on the other.
- 106 • 8 mg/4 mg – red, gsk debossed on one side and 8/4 on the other.

## 107 **4 CONTRAINDICATIONS**

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

110 **5 WARNINGS AND PRECAUTIONS**

111 **5.1 Increased Risk of Cardiovascular Mortality for Sulfonylurea Drugs**

112 The administration of oral hypoglycemic drugs has been reported to be associated  
113 with increased cardiovascular mortality as compared to treatment with diet alone or diet  
114 plus insulin. This warning is based on the trial conducted by the University Group Diabetes  
115 Program (UGDP), a long-term, prospective clinical trial designed to evaluate the  
116 effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in  
117 patients with non-insulin-dependent diabetes. The trial involved 823 patients who were  
118 randomly assigned to one of four treatment groups (*Diabetes* 1970;19[Suppl. 2]:747-830).  
119 UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of  
120 tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately  
121 2½ times that of patients treated with diet alone. A significant increase in total mortality  
122 was not observed, but the use of tolbutamide was discontinued based on the increase in  
123 cardiovascular mortality, thus limiting the opportunity for the trial to show an increase in  
124 overall mortality. Despite controversy regarding the interpretation of these results, the  
125 findings of the UGDP trial provide an adequate basis for this warning. The patient should  
126 be informed of the potential risks and advantages of glimepiride-containing tablets and of  
127 alternative modes of therapy.

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

132 **5.2 Cardiac Failure With Rosiglitazone**

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

139 Patients with congestive heart failure (CHF) NYHA Class I and II treated with  
140 rosiglitazone have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-  
141 controlled echocardiographic trial was conducted in 224 patients with type 2 diabetes mellitus  
142 and NYHA Class I or II CHF (ejection fraction ≤45%) on background antidiabetic and CHF  
143 therapy. An independent committee conducted a blinded evaluation of fluid-related events  
144 (including congestive heart failure) and cardiovascular hospitalizations according to predefined  
145 criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were  
146 reported by investigators. Although no treatment difference in change from baseline of ejection  
147 fractions was observed, more cardiovascular adverse events were observed with rosiglitazone  
148 treatment compared to placebo during the 52-week trial. (See Table 1.)

149

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

Events	Rosiglitazone	Placebo
	N = 110	N = 114
	n (%)	n (%)
<b>Adjudicated</b>		
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 <sup>a</sup>	21 (19%)	15 (13%)
<b>Investigator-reported, non-adjudicated</b>		
Ischemic adverse events	10 (9%)	5 (4%)
– Myocardial infarction	5 (5%)	2 (2%)
– Angina	6 (5%)	3 (3%)

153 <sup>a</sup> Includes hospitalization for any cardiovascular reason.  
 154

155 Initiation of AVANDARYL in patients with established NYHA Class III or IV heart  
 156 failure is contraindicated. AVANDARYL is not recommended in patients with symptomatic  
 157 heart failure. [See **Boxed Warning**.]

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

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

166 **Congestive Heart Failure During Coadministration of Rosiglitazone With Insulin:**

167 In trials in which rosiglitazone was added to insulin, rosiglitazone increased the risk of  
 168 congestive heart failure. Coadministration of rosiglitazone and insulin is not recommended. [See  
 169 *Indications and Usage (1) and Warnings and Precautions (5.3).*]

170 In 7 controlled, randomized, double-blind trials which had durations from 16 to 26 weeks  
 171 and which were included in a meta-analysis<sup>1</sup> [see *Warnings and Precautions (5.3)*], patients with  
 172 type 2 diabetes mellitus were randomized to coadministration of rosiglitazone and insulin

173 (N = 1,018) or insulin (N = 815). In these 7 trials, rosiglitazone was added to insulin. These trials  
174 included patients with long-standing diabetes (median duration of 12 years) and a high  
175 prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy,  
176 ischemic heart disease, vascular disease, and congestive heart failure. The total number of  
177 patients with emergent congestive heart failure was 23 (2.3%) and 8 (1.0%) in the rosiglitazone  
178 plus insulin and insulin groups, respectively.

179 Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing  
180 Rosiglitazone to Pioglitazone: Three observational studies<sup>2-4</sup> in elderly diabetic patients (age  
181 65 years and older) found that rosiglitazone statistically significantly increased the risk of  
182 hospitalized heart failure compared to use of pioglitazone. One other observational study<sup>5</sup> in  
183 patients with a mean age of 54 years, which also included an analysis in a subpopulation of  
184 patients >65 years of age, found no statistically significant increase in emergency department  
185 visits or hospitalization for heart failure in patients treated with rosiglitazone compared to  
186 pioglitazone in the older subgroup.

### 187 **5.3 Major Adverse Cardiovascular Events**

188 Cardiovascular adverse events have been evaluated in a meta-analysis of 52 clinical  
189 trials, in long-term, prospective, randomized, controlled trials, and in observational studies.

190 Meta-Analysis of Major Adverse Cardiovascular Events in a Group of 52 Clinical  
191 Trials: A meta-analysis was conducted retrospectively to assess cardiovascular adverse events  
192 reported across 52 double-blind, randomized, controlled clinical trials (mean duration 6  
193 months).<sup>1</sup> These trials had been conducted to assess glucose-lowering efficacy in type 2 diabetes.  
194 Prospectively planned adjudication of cardiovascular events did not occur in most of the trials.  
195 Some trials were placebo-controlled and some used active oral antidiabetic drugs as controls.  
196 Placebo-controlled trials included monotherapy trials (monotherapy with rosiglitazone versus  
197 placebo monotherapy) and add-on trials (rosiglitazone or placebo, added to sulfonylurea,  
198 metformin, or insulin). Active control trials included monotherapy trials (monotherapy with  
199 rosiglitazone versus sulfonylurea or metformin monotherapy) and add-on trials (rosiglitazone  
200 plus sulfonylurea or rosiglitazone plus metformin, versus sulfonylurea plus metformin). A total  
201 of 16,995 patients were included (10,039 in treatment groups containing rosiglitazone, 6,956 in  
202 comparator groups), with 5,167 patient-years of exposure to rosiglitazone and 3,637 patient-  
203 years of exposure to comparator. Cardiovascular events occurred more frequently for patients  
204 who received rosiglitazone than for patients who received comparators (see Table 2).  
205



206 **Table 2. Occurrence of Cardiovascular Events in a Meta-Analysis of 52 Clinical Trials**

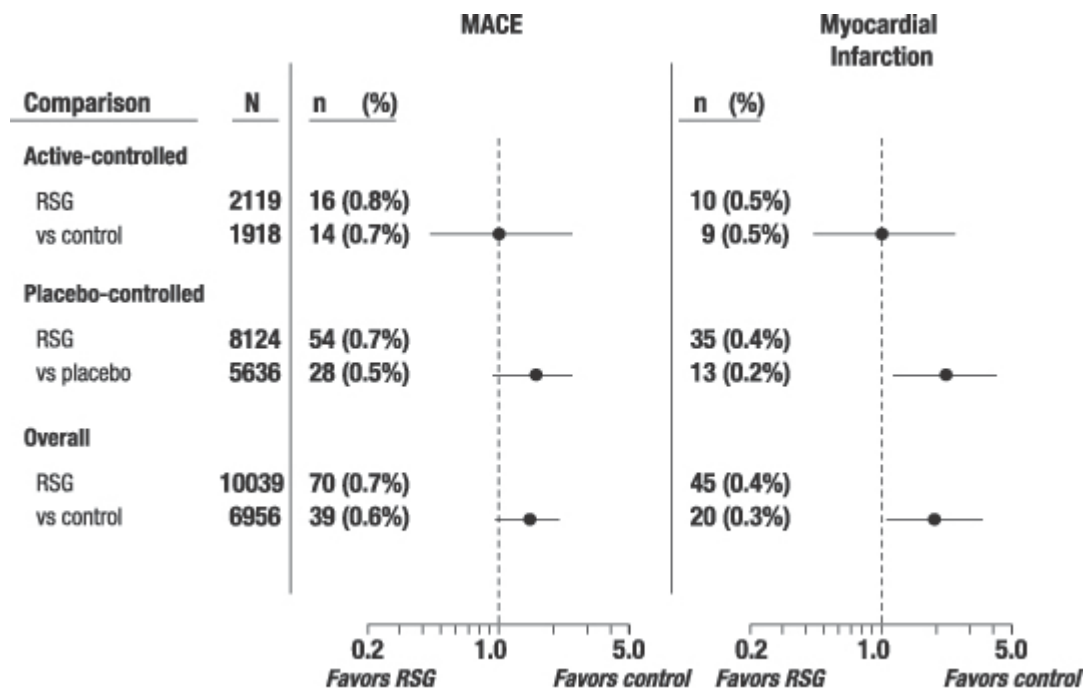
<b>Event<sup>a</sup></b>	<b>Rosiglitazone (N=10,039) n (%)</b>	<b>Comparator (N=6,956) n (%)</b>
MACE (a composite of myocardial infarction, cardiovascular death, or stroke)	70 (0.7)	39 (0.6)
Myocardial Infarction	45 (0.4)	20 (0.3)
Cardiovascular Death	17 (0.2)	9 (0.1)
Stroke	18 (0.2)	16 (0.2)
All-cause Death	29 (0.3)	17 (0.2)

207 <sup>a</sup> Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial  
 208 infarction would be counted in 4 event categories (myocardial infarction; myocardial  
 209 infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).

210  
 211 In this analysis, a statistically significant increased risk of myocardial infarction with  
 212 rosiglitazone versus pooled comparators was observed. Analyses were performed using a  
 213 composite of major adverse cardiovascular events (myocardial infarction, stroke, and  
 214 cardiovascular death), referred to hereafter as MACE. Rosiglitazone had a statistically non-  
 215 significant increased risk of MACE compared to the pooled comparators. A statistically  
 216 significant increased risk of myocardial infarction and statistically non-significant increased risk  
 217 of MACE with rosiglitazone was observed in the placebo-controlled trials. In the active-  
 218 controlled trials, there was no increased risk of myocardial infarction or MACE. (See Figure 1  
 219 and Table 3.)  
 220

221  
222  
223

**Figure 1. Forest Plot of Odds Ratios (95% Confidence Intervals) for MACE and Myocardial Infarction in the Meta-Analysis of 52 Clinical Trials**



224  
225

RSG = rosiglitazone

226  
227

**Table 3. Occurrence of MACE and Myocardial Infarction in a Meta-Analysis of 52 Clinical Trials by Trial Type**

		MACE			Myocardial Infarction	
		N	n (%)	OR (95% CI)	n (%)	OR (95% CI)
<b>Active-Controlled Trials</b>	RSG	2,119	16 (0.8%)	1.05 (0.48, 2.34)	10 (0.5%)	1.00 (0.36, 2.82)
	Control	1,918	14 (0.7%)		9 (0.5%)	
<b>Placebo-Controlled Trials</b>	RSG	8,124	54 (0.7%)	1.53 (0.94, 2.54)	35 (0.4%)	2.23 (1.14, 4.64)
	Placebo	5,636	28 (0.5%)		13 (0.2%)	
<b>Overall</b>	RSG	10,039	70 (0.7%)	1.44 (0.95, 2.20)	45 (0.4%)	1.8 (1.03, 3.25)
	Control	6,956	39 (0.6%)		20 (0.3%)	

228  
229

RSG = rosiglitazone

230  
231  
232  
233  
234

Of the placebo-controlled trials in the meta-analysis, 7 trials had patients randomized to rosiglitazone plus insulin or insulin. There were more patients in the rosiglitazone plus insulin group compared to the insulin group with myocardial infarctions, MACE, cardiovascular deaths, and all-cause deaths (see Table 4). The total number of patients with stroke was 5 (0.5%) and 4 (0.5%) in the rosiglitazone plus insulin and insulin groups, respectively. The use of rosiglitazone

235 in combination with insulin may increase the risk of myocardial infarction [See Warnings and  
 236 Precautions (5.1).]  
 237

238 **Table 4. Occurrence of Cardiovascular Events for Rosiglitazone in Combination With**  
 239 **Insulin in a Meta-Analysis of 52 Clinical Trials**

Event <sup>a</sup>	Rosiglitazone (N=1,018) (%)	Insulin (N = 815) (%)	OR (95% CI)
MACE (a composite of myocardial infarction, cardiovascular death, or stroke)	1.3	0.6	2.14 (0.70, 7.83)
Myocardial infarction	0.6	0.1	5.6 (0.67, 262.7)
Cardiovascular death	0.4	0.0	ND, (0.47, ∞)
All cause death	0.6	0.2	2.19 (0.38, 22.61)

240 ND = not defined

241 <sup>a</sup> Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial  
 242 infarction would be counted in 4 event categories (myocardial infarction; myocardial  
 243 infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).  
 244

245 Myocardial Infarction Events in Large, Long-Term, Prospective, Randomized,  
 246 Controlled Trials of Rosiglitazone: Data from 3 large, long-term, prospective, randomized,  
 247 controlled clinical trials of rosiglitazone were assessed separately from the meta-analysis.<sup>6-8</sup>  
 248 These 3 trials included a total of 14,067 patients (treatment groups containing rosiglitazone  
 249 N = 6,311; comparator groups N = 7,756), with patient-year exposure of 24,534 patient-years for  
 250 rosiglitazone and 28,882 patient-years for comparator. Patient populations in the trials included  
 251 patients with impaired glucose tolerance, patients with type 2 diabetes who were initiating oral  
 252 agent monotherapy, and patients with type 2 diabetes who had failed monotherapy and were  
 253 initiating dual oral agent therapy. Duration of follow-up exceeded 3 years in each trial.

254 In each of these trials, there was a statistically non-significant increase in the risk of  
 255 myocardial infarction for rosiglitazone versus comparator medications.

256 In a long-term, randomized, placebo-controlled, 2x2 factorial trial intended to evaluate  
 257 rosiglitazone, and separately ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on  
 258 progression to overt diabetes in 5,269 subjects with glucose intolerance, the incidence of  
 259 myocardial infarction was higher in the subset of subjects who received rosiglitazone in  
 260 combination with ramipril than among subjects who received ramipril alone but not in the subset  
 261 of subjects who received rosiglitazone alone compared to placebo.<sup>6</sup> The higher incidence of  
 262 myocardial infarction among subjects who received rosiglitazone in combination with ramipril  
 263 was not confirmed in the two other large (total N = 8,798) long-term, randomized, active-  
 264 controlled clinical trials conducted in patients with type 2 diabetes, in which 30% and 40% of  
 265 patients in the two trials reported angiotensin-converting enzyme inhibitor use at baseline.<sup>7,8</sup>

266 There have been no adequately designed clinical trials directly comparing rosiglitazone to  
267 pioglitazone on cardiovascular risks. However, in a long-term, randomized, placebo-controlled  
268 cardiovascular outcomes trial comparing pioglitazone to placebo in patients with type 2 diabetes  
269 mellitus and prior macrovascular disease, pioglitazone was not associated with an increased risk  
270 of myocardial infarction or total mortality.<sup>9</sup>

271 The increased risk of myocardial infarction observed in the meta-analysis and large, long-  
272 term controlled clinical trials, and the increased risk of MACE observed in the meta-analysis  
273 described above, have not translated into a consistent finding of excess mortality from controlled  
274 clinical trials or observational studies. Clinical trials have not shown any difference between  
275 rosiglitazone and comparator medications in overall mortality or CV-related mortality.

#### 276 Mortality in Observational Studies of Rosiglitazone Compared to Pioglitazone:

277 Three observational studies in elderly diabetic patients (age 65 years and older) found that  
278 rosiglitazone statistically significantly increased the risk of all-cause mortality compared to use  
279 of ACTOS (pioglitazone).<sup>2-4</sup> One observational study<sup>5</sup> in patients with a mean age of 54 years  
280 found no difference in all-cause mortality between patients treated with rosiglitazone compared  
281 to ACTOS (pioglitazone) and reported similar results in the subpopulation of patients >65 years  
282 of age. One additional small, prospective, observational study<sup>10</sup> found no statistically significant  
283 differences for CV mortality and all-cause mortality in patients treated with rosiglitazone  
284 compared to ACTOS (pioglitazone).

### 285 **5.4 Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program**

286 Because of the potential increased risk of myocardial infarction, AVANDARYL is  
287 available only through a restricted distribution program called the AVANDIA-Rosiglitazone  
288 Medicines Access Program [see *Indications and Usage (1)*]. Both prescribers and patients must  
289 enroll in the program to be able to prescribe or receive AVANDARYL, respectively.  
290 AVANDARYL will be available only from specially certified pharmacies participating in the  
291 program. As part of the program, prescribers will be educated about the potential increased risk  
292 of myocardial infarction and the need to limit the use of AVANDARYL to eligible patients.  
293 Prescribers will need to discuss with patients the risks and benefits of taking AVANDARYL. To  
294 enroll, call 1-800-AVANDIA or visit [www.AVANDIA.com](http://www.AVANDIA.com).

### 295 **5.5 Hypoglycemia**

296 AVANDARYL is a combination tablet containing rosiglitazone and glimepiride, a  
297 sulfonylurea. All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper  
298 patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Elderly  
299 patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs.  
300 Debilitated or malnourished patients, and those with adrenal, pituitary, renal, or hepatic  
301 insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs.  
302 A starting dose of 1 mg glimepiride, as contained in AVANDARYL 4 mg/1 mg, followed by  
303 appropriate dose titration is recommended in these patients. [See *Clinical Pharmacology (12.3)*.]  
304 Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-  
305 adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur

306 when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or  
307 when more than one glucose-lowering drug is used.

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

## 311 **5.6 Edema**

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

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

320 In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was  
321 reported in patients treated with rosiglitazone, and may be dose-related. Patients with ongoing  
322 edema were more likely to have adverse events associated with edema if started on combination  
323 therapy with insulin and rosiglitazone [*see Adverse Reactions (6.1)*]. The use of AVANDARYL  
324 in combination with insulin is not recommended [*see Warnings and Precautions (5.2, 5.3)*].

## 325 **5.7 Weight Gain**

326 Dose-related weight gain was seen with AVANDARYL, rosiglitazone alone, and  
327 rosiglitazone together with other hypoglycemic agents (see Table 5). The mechanism of weight  
328 gain is unclear but probably involves a combination of fluid retention and fat accumulation.  
329

330 Table 5. Weight Changes (kg) From Baseline at Endpoint During Clinical Trials  
 [Median (25<sup>th</sup>, 75<sup>th</sup>, Percentile)]

<b>Monotherapy</b>				
<b>Duration</b>	<b>Control Group</b>		<b>Rosiglitazone 4 mg</b>	<b>Rosiglitazone 8 mg</b>
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
<b>Combination Therapy</b>				
			<b>Rosiglitazone + Control Therapy</b>	
<b>Duration</b>	<b>Control Group</b>		<b>Rosiglitazone 4 mg</b>	<b>Rosiglitazone 8 mg</b>
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

331  
 332 In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed  
 333 with type 2 diabetes not previously treated with antidiabetic medication, the median weight  
 334 change (25<sup>th</sup>, 75<sup>th</sup> percentiles) from baseline at 4 years was 3.5 kg (0.0, 8.1) for rosiglitazone,  
 335 2.0 kg (-1.0, 4.8) for glyburide, and -2.4 kg (-5.4, 0.5) for metformin.

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

341 **5.8 Hepatic Effects**

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

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

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

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

### 362 **5.9 Macular Edema**

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

### 373 **5.10 Fractures**

374 In a 4- to 6-year comparative trial (ADOPT) of glycemic control with monotherapy in  
375 drug-naïve patients recently diagnosed with type 2 diabetes mellitus, an increased incidence of  
376 bone fracture was noted in female patients taking rosiglitazone. Over the 4- to 6-year period, the  
377 incidence of bone fracture in females was 9.3% (60/645) for rosiglitazone versus 3.5% (21/605)  
378 for glyburide and 5.1% (30/590) for metformin. This increased incidence was noted after the first  
379 year of treatment and persisted during the course of the trial. The majority of the fractures in the  
380 women who received rosiglitazone occurred in the upper arm, hand, and foot. These sites of  
381 fracture are different from those usually associated with postmenopausal osteoporosis (e.g., hip  
382 or spine). Other trials suggest that this risk may also apply to men, although the risk of fracture  
383 among women appears higher than that among men. The risk of fracture should be considered in  
384 the care of patients treated with rosiglitazone, and attention given to assessing and maintaining  
385 bone health according to current standards of care.

### 386 **5.11 Hematologic Effects**

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

### 390 **5.12 Hemolytic Anemia**

391 Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with  
392 sulfonylurea agents can lead to hemolytic anemia. Because glimepiride, a component of  
393 AVANDARYL, belongs to the class of sulfonylurea agents, caution should be used in patients

394 with G6PD deficiency and a non-sulfonylurea alternative should be considered. In post-  
395 marketing experience, hemolytic anemia has also been reported in patients receiving  
396 sulfonylureas who did not have known G6PD deficiency [see *Adverse Reactions (6.1)*].

### 397 **5.13 Diabetes and Blood Glucose Control**

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

402 Periodic fasting glucose and HbA1c measurements should be performed to monitor  
403 therapeutic response.

### 404 **5.14 Ovulation**

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

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

## 414 **6 ADVERSE REACTIONS**

### 415 **6.1 Clinical Trial Experience**

416 Because clinical trials are conducted under widely varying conditions, adverse reaction  
417 rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical  
418 trials of another drug and may not reflect the rates observed in practice.

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

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

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



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

440 In 26-week double-blind, fixed-dose trials, edema was reported with higher frequency in  
441 the rosiglitazone plus insulin combination trials (insulin, 5.4%; and rosiglitazone in combination  
442 with insulin, 14.7%). Reports of new onset or exacerbation of congestive heart failure occurred  
443 at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with  
444 rosiglitazone [see **Boxed Warning and Warnings and Precautions (5.2)**]. The use of  
445 rosiglitazone in combination with insulin may increase the risk of myocardial infarction [see  
446 **Warnings and Precautions (5.3)**].

447 **Glimepiride: Hypoglycemia:** The incidence of hypoglycemia with glimepiride, as  
448 documented by blood glucose values <60 mg/dL, ranged from 0.9% to 1.7% in 2 large, well-  
449 controlled, 1-year trials. In patients treated with glimepiride in US placebo-controlled trials  
450 (N = 746), adverse events, other than hypoglycemia, considered to be possibly or probably  
451 related to trial drug that occurred in more than 1% of patients included dizziness (1.7%), asthenia  
452 (1.6%), headache (1.5%), and nausea (1.1%).

453 **Gastrointestinal Reactions:** Vomiting, gastrointestinal pain, and diarrhea have been  
454 reported, but the incidence in placebo-controlled trials was less than 1%. In rare cases, there may  
455 be an elevation of liver enzyme levels. In isolated instances, impairment of liver function (e.g.,  
456 with cholestasis and jaundice), as well as hepatitis, which may also lead to liver failure have been  
457 reported with sulfonylureas, including glimepiride.

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

464 **Hematologic Reactions:** Leukopenia, agranulocytosis, thrombocytopenia, hemolytic  
465 anemia [see **Warnings and Precautions (5.12)**], aplastic anemia, and pancytopenia have been  
466 reported with sulfonylureas, including glimepiride.

467 **Metabolic Reactions:** Hepatic porphyria reactions and disulfiram-like reactions have  
468 been reported with sulfonylureas, including glimepiride. Cases of hyponatremia have been  
469 reported with glimepiride and all other sulfonylureas, most often in patients who are on other  
470 medications or have medical conditions known to cause hyponatremia or increase release of  
471 antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion

472 has been reported with certain other sulfonylureas, including glimepiride, and it has been  
473 suggested that certain sulfonylureas may augment the peripheral (antidiuretic) action of ADH  
474 and/or increase release of ADH.

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

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

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

495 In ADOPT, fractures were reported in a greater number of women treated with  
496 rosiglitazone (9.3%, 2.7/100 patient-years) compared to glyburide (3.5%, 1.3/100 patient-years)  
497 or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who  
498 received rosiglitazone were reported in the upper arm, hand, and foot. [See *Warnings and*  
499 *Precautions (5.10)*.] The observed incidence of fractures for male patients was similar among the  
500 3 treatment groups.

501

502 **Table 6. On-Therapy Adverse Events (≥5 Events/100 Patient-Years [PY]) in Any**  
 503 **Treatment Group Reported in a 4- to 6-Year Clinical Trial of Rosiglitazone as**  
 504 **Monotherapy (ADOPT)**

	<b>Rosiglitazone</b> N = 1,456 PY = 4,954	<b>Glyburide</b> N = 1,441 PY = 4,244	<b>Metformin</b> 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

505

506 **6.2 Laboratory Abnormalities**

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

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

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

521 In pre-approval controlled trials, 0.2% of patients treated with rosiglitazone had  
 522 reversible elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and  
 523 0.5% on active comparators. The ALT elevations in patients treated with rosiglitazone were  
 524 reversible. Hyperbilirubinemia was found in 0.3% of patients treated with rosiglitazone  
 525 compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In  
 526 pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic  
 527 failure. [See *Warnings and Precautions (5.8)*.]

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

532 **6.3 Postmarketing Experience**

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

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

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

545 There are postmarketing reports with rosiglitazone of rash, pruritus, urticaria,  
546 angioedema, anaphylactic reaction, Stevens-Johnson syndrome, and new onset or worsening  
547 diabetic macular edema with decreased visual acuity [*see **Warnings and Precautions (5.9)***].

548 **7 DRUG INTERACTIONS**

549 **7.1 Drugs Metabolized by Cytochrome P450**

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

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

560 **7.2 Drugs That Produce Hyperglycemia**

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

567 **8 USE IN SPECIFIC POPULATIONS**

568 **8.1 Pregnancy**

569 Pregnancy Category C.

570 All pregnancies have a background risk of birth defects, loss, or other adverse outcome  
571 regardless of drug exposure. This background risk is increased in pregnancies complicated by  
572 hyperglycemia and may be decreased with good metabolic control. It is essential for patients  
573 with diabetes or history of gestational diabetes to maintain good metabolic control before  
574 conception and throughout pregnancy. Careful monitoring of glucose control is essential in such  
575 patients. Most experts recommend that insulin monotherapy be used during pregnancy to  
576 maintain blood glucose levels as close to normal as possible. AVANDARYL should not be used  
577 during pregnancy.

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

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

585 *Rosiglitazone:* There was no effect on implantation or the embryo with rosiglitazone  
586 treatment during early pregnancy in rats, but treatment during mid-late gestation was associated  
587 with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed  
588 at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human  
589 AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused  
590 placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation  
591 reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible  
592 after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was  
593 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately  
594 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced  
595 the number of uterine implantations and live offspring when juvenile female rats were treated at  
596 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human  
597 AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day  
598 (approximately 4 times human AUC at the maximum recommended daily dose). There was no  
599 effect on pre- or post-natal survival or growth.

600 *Glimepiride:* Glimepiride did not produce teratogenic effects in rats exposed orally up to  
601 4,000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose  
602 based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately  
603 60 times the maximum recommended human dose based on surface area). Glimepiride has been  
604 shown to be associated with intrauterine fetal death in rats when given in doses as low as  
605 50 times the human dose based on surface area and in rabbits when given in doses as low as  
606 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses  
607 inducing maternal hypoglycemia, has been similarly noted with other sulfonyleureas, and is  
608 believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

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

## 617 **8.2 Labor and Delivery**

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

## 620 **8.3 Nursing Mothers**

621 No trials have been conducted with AVANDARYL. It is not known whether  
622 rosiglitazone or glimepiride is excreted in human milk. Because many drugs are excreted in  
623 human milk, AVANDARYL should not be administered to a nursing woman.

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

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

## 629 **8.4 Pediatric Use**

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

## 633 **8.5 Geriatric Use**

634 Rosiglitazone: Results of the population pharmacokinetic analysis showed that age does  
635 not significantly affect the pharmacokinetics of rosiglitazone [*see Clinical Pharmacology*  
636 (12.3)]. Therefore, no dosage adjustments are required for the elderly. In controlled clinical  
637 trials, no overall differences in safety and effectiveness between older ( $\geq 65$  years) and younger  
638 ( $< 65$  years) patients were observed.

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

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

646 The drug is known to be substantially excreted by the kidney, and the risk of toxic  
647 reactions to this drug may be greater in patients with impaired renal function. Because elderly

648 patients are more likely to have decreased renal function, care should be taken in dose selection,  
649 and it may be useful to monitor renal function.

650 Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering  
651 drugs. In elderly, debilitated, or malnourished patients, or in patients with renal, hepatic or  
652 adrenal insufficiency, the starting dose, dose increments, and maintenance dosage should be  
653 conservative based upon blood glucose levels prior to and after initiation of treatment to avoid  
654 hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly and in people  
655 who are taking beta-adrenergic blocking drugs or other sympatholytic agents [see *Dosage and*  
656 *Administration (2.4), Warnings and Precautions (5.5), and Clinical Pharmacology (12.3)*].

## 657 **10 OVERDOSAGE**

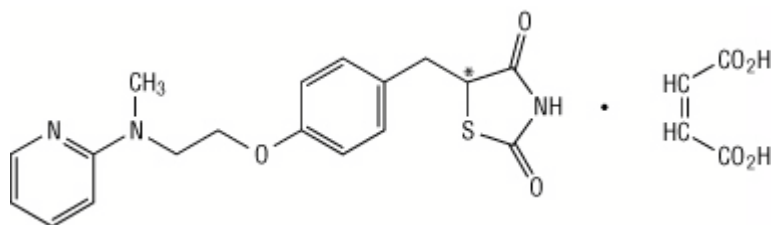
658 **Rosiglitazone:** Limited data are available with regard to overdosage in humans. In  
659 clinical trials in volunteers, rosiglitazone has been administered at single oral doses of up to  
660 20 mg and was well tolerated. In the event of an overdose, appropriate supportive treatment  
661 should be initiated as dictated by the patient's clinical status.

662 **Glimepiride:** Overdosage of sulfonylureas, including glimepiride, can produce  
663 hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic  
664 findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or  
665 meal patterns. Close monitoring should continue until the physician is assured that the patient is  
666 out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological  
667 impairment occur infrequently, but constitute medical emergencies requiring immediate  
668 hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a  
669 rapid IV injection of concentrated (50%) glucose solution. This should be followed by a  
670 continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood  
671 glucose level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to  
672 48 hours, because hypoglycemia may recur after apparent clinical recovery.

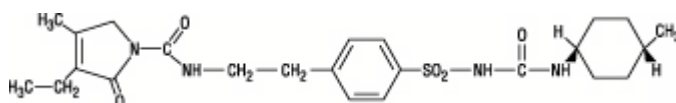
## 673 **11 DESCRIPTION**

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

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



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



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

## 701 12 CLINICAL PHARMACOLOGY

### 702 12.1 Mechanism of Action

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

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

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



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

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

## 737 **12.2 Pharmacodynamics**

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

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

## 748 **12.3 Pharmacokinetics**

749 In a bioequivalence trial of AVANDARYL 4 mg/4 mg, the area under the curve (AUC)  
750 and maximum concentration ( $C_{max}$ ) of rosiglitazone following a single dose of the combination  
751 tablet were bioequivalent to rosiglitazone 4 mg concomitantly administered with glimepiride  
752 4 mg under fasted conditions. The AUC of glimepiride following a single fasted 4 mg/4 mg dose  
753 was equivalent to glimepiride concomitantly administered with rosiglitazone, while the  $C_{max}$  was  
754 13% lower when administered as the combination tablet (see Table 7).

755

756 Table 7. Pharmacokinetic Parameters for Rosiglitazone and Glimepiride (N = 28)

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

757 AUC = area under the curve; C<sub>max</sub> = maximum concentration; T<sub>1/2</sub> = terminal half-life;758 T<sub>max</sub> = time of maximum concentration.759 Regimen A = AVANDARYL 4 mg/4 mg tablet; Regimen B = Concomitant dosing of a  
760 rosiglitazone 4 mg tablet AND a glimepiride 4 mg tablet.761 Data presented as geometric mean (range), except T<sub>1/2</sub> which is presented as arithmetic mean  
762 (range) and T<sub>max</sub>, which is presented as median (range).

763

764 The rate and extent of absorption of both the rosiglitazone component and glimepiride  
765 component of AVANDARYL when taken with food were equivalent to the rate and extent of  
766 absorption of rosiglitazone and glimepiride when administered concomitantly as separate tablets  
767 with food.768 Absorption: The AUC and C<sub>max</sub> of glimepiride increased in a dose-proportional manner  
769 following administration of AVANDARYL 4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg.770 Administration of AVANDARYL in the fed state resulted in no change in the overall exposure  
771 of rosiglitazone; however, the C<sub>max</sub> of rosiglitazone decreased by 32% compared to the fasted  
772 state. There was an increase in both AUC (19%) and C<sub>max</sub> (55%) of glimepiride in the fed state  
773 compared to the fasted state.774 *Rosiglitazone:* The absolute bioavailability of rosiglitazone is 99%. Peak plasma  
775 concentrations are observed about 1 hour after dosing. The C<sub>max</sub> and AUC of rosiglitazone  
776 increase in a dose-proportional manner over the therapeutic dose range.777 *Glimepiride:* After oral administration, glimepiride is completely (100%) absorbed from  
778 the gastrointestinal tract. Trials with single oral doses in normal subjects and with multiple oral  
779 doses in patients with type 2 diabetes have shown significant absorption of glimepiride within  
780 1 hour after administration and C<sub>max</sub> at 2 to 3 hours.

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

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

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

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

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

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

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

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

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

825 *Geriatric: Rosiglitazone:* Results of the population pharmacokinetics analysis (N = 716  
826 <65 years; N = 331 ≥65 years) showed that age does not significantly affect the  
827 pharmacokinetics of rosiglitazone.

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

835 *Hepatic Impairment:* Therapy with AVANDARYL should not be initiated if the patient  
836 exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT  
837 >2.5X upper limit of normal) at baseline [see Warnings and Precautions (5.8)].

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

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

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

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

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

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

861 increased 2.3 and 8.6 times from Group I to Group III. The apparent terminal half-life ( $T_{1/2}$ ) for  
862 glimepiride did not change, while the half-lives for M1 and M2 increased as renal function  
863 decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased  
864 (44.4%, 21.9%, and 9.3% for Groups I to III). A multiple-dose titration trial was also conducted  
865 in 16 type 2 diabetes patients with renal impairment using doses ranging from 1 to 8 mg daily for  
866 3 months. The results were consistent with those observed after single doses. All patients with a  
867  $CL_{cr}$  less than 22 mL/min had adequate control of their glucose levels with a dosage regimen of  
868 only 1 mg daily. The results from this trial suggest that a starting dose of 1 mg glimepiride, as  
869 contained in AVANDARYL 4 mg/1 mg, may be given to type 2 diabetes patients with kidney  
870 disease, and the dose may be titrated based on fasting glucose levels.

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

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

879 *Glimepiride:* The pharmacokinetics of glimepiride (1 mg) were evaluated in a single-  
880 dose trial conducted in 30 type 2 diabetic patients (male = 7; female = 23) between ages 10 and  
881 17 years. The mean  $AUC_{0-last}$  ( $338.8 \pm 203.1$  ng.hr/mL),  $C_{max}$  ( $102.4 \pm 47.7$  ng/mL), and  $T_{1/2}$   
882 ( $3.1 \pm 1.7$  hours) were comparable to those previously reported in adults ( $AUC_{0-last}$   
883  $315.2 \pm 95.9$  ng.hr/mL,  $C_{max}$   $103.2 \pm 34.3$  ng/mL, and  $T_{1/2}$   $5.3 \pm 4.1$  hours).

#### 884 **12.4 Drug-Drug Interactions**

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

889 Rosiglitazone: Drugs That Inhibit, Induce or are Metabolized by Cytochrome  
890 *P450:* In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the  
891 major P450 enzymes at clinically relevant concentrations. In vitro data demonstrate that  
892 rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9. [See *Drug*  
893 *Interactions (7.1).*]

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

897 *Gemfibrozil:* Concomitant administration of gemfibrozil (600 mg twice daily), an  
898 inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone  
899 AUC by 127%, compared to the administration of rosiglitazone (4 mg once daily) alone. Given

900 the potential for dose-related adverse events with rosiglitazone, a decrease in the dose of  
901 rosiglitazone may be needed when gemfibrozil is introduced [see Drug Interactions (7.1)].

902 **Rifampin:** Rifampin administration (600 mg once a day), an inducer of CYP2C8, for  
903 6 days is reported to decrease rosiglitazone AUC by 66%, compared to the administration of  
904 rosiglitazone (8 mg) alone [see Drug Interactions (7.1)].<sup>11</sup>

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

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

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

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

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

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

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

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

939 *H<sub>2</sub>-Receptor Antagonists:* Coadministration of either cimetidine (800 mg once daily) or  
940 ranitidine (150 mg twice daily) with a single 4-mg oral dose of glimepiride did not significantly  
941 alter the absorption and disposition of glimepiride, and no differences were seen in  
942 hypoglycemic symptomatology.

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

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

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

962 *Other:* Although no specific interaction trials were performed, pooled data from clinical  
963 trials showed no evidence of clinically significant adverse interactions with uncontrolled  
964 concurrent administration of aspirin and other salicylates, H<sub>2</sub>-receptor antagonists, ACE  
965 inhibitors, calcium-channel blockers, estrogens, fibrates, NSAIDs, HMG CoA reductase  
966 inhibitors, sulfonamides, or thyroid hormone.

## 967 **13 NONCLINICAL TOXICOLOGY**

### 968 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

985 **Mutagenesis:** Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial  
986 assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in  
987 vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about  
988 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic  
989 activation.

990 **Impairment of Fertility:** Rosiglitazone had no effects on mating or fertility of male rats  
991 given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended  
992 human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility  
993 (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and  
994 estradiol (approximately 20 and 200 times human AUC at the maximum recommended human  
995 daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times  
996 human AUC at the maximum recommended human daily dose). In juvenile rats dosed from  
997 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male  
998 reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in  
999 females (approximately 68 times human AUC at the maximum recommended daily dose). In  
1000 monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at  
1001 the maximum recommended human daily dose, respectively) diminished the follicular phase rise  
1002 in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal  
1003 phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct  
1004 inhibition of ovarian steroidogenesis.

1005 **Glimepiride: Carcinogenesis:** Studies in rats at doses of up to 5,000 parts per million  
1006 (ppm) in complete feed (approximately 340 times the maximum recommended human dose,  
1007 based on surface area) for 30 months showed no evidence of carcinogenesis. In mice,  
1008 administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma  
1009 formation which was dose-related and is thought to be the result of chronic pancreatic  
1010 stimulation. The no-effect dose for adenoma formation in mice in this study was 320 ppm in  
1011 complete feed, or 46 to 54 mg/kg body weight/day. This is about 35 times the maximum human  
1012 recommended dose based on surface area.

1013 **Mutagenesis:** Glimepiride was non-mutagenic in a battery of in vitro and in vivo  
1014 mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled  
1015 DNA synthesis, mouse micronucleus test).

1016 **Impairment of Fertility:** There was no effect of glimepiride on male mouse fertility in  
1017 animals exposed up to 2,500 mg/kg body weight ( $>1,700$  times the maximum recommended



1018 human dose based on surface area). Glimepiride had no effect on the fertility of male and female  
1019 rats administered up to 4,000 mg/kg body weight (approximately 4,000 times the maximum  
1020 recommended human dose based on surface area).

### 1021 **13.2 Animal Toxicology and/or Pharmacology**

1022 Rosiglitazone: Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day),  
1023 and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human  
1024 AUC at the maximum recommended human daily dose, respectively). Effects in juvenile rats  
1025 were consistent with those seen in adults. Morphometric measurement indicated that there was  
1026 hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result  
1027 of plasma volume expansion.

1028 Glimepiride: Reduced serum glucose values and degranulation of the pancreatic beta  
1029 cells were observed in beagle dogs exposed to glimepiride 320 mg/kg/day for 12 months  
1030 (approximately 1,000 times the recommended human dose based on surface area). No evidence  
1031 of tumor formation was observed in any organ. One female and one male dog developed bilateral  
1032 subcapsular cataracts. Non-GLP studies indicated that glimepiride was unlikely to exacerbate  
1033 cataract formation. Evaluation of the co-cataractogenic potential of glimepiride in several  
1034 diabetic and cataract rat models was negative and there was no adverse effect of glimepiride on  
1035 bovine ocular lens metabolism in organ culture [*see Adverse Reactions (6.1)*].

## 1036 **14 CLINICAL STUDIES**

1037 The safety and efficacy of rosiglitazone added to a sulfonylurea have been studied in  
1038 clinical trials in patients with type 2 diabetes inadequately controlled on sulfonylureas alone. No  
1039 clinical trials have been conducted with the fixed-dose combination of AVANDARYL in  
1040 patients inadequately controlled on a sulfonylurea or who have initially responded to  
1041 rosiglitazone alone and require additional glycemic control.

1042 A total of 3,457 patients with type 2 diabetes participated in ten 24- to 26-week  
1043 randomized, double-blind, placebo/active-controlled trials and one 2-year double-blind, active-  
1044 controlled trial in elderly patients designed to assess the efficacy and safety of rosiglitazone in  
1045 combination with a sulfonylurea. Rosiglitazone 2 mg, 4 mg, or 8 mg daily, was administered  
1046 either once daily (3 trials) or in divided doses twice daily (7 trials), to patients inadequately  
1047 controlled on a submaximal or maximal dose of sulfonylurea.

1048 In these trials, the combination of rosiglitazone 4 mg or 8 mg daily (administered as  
1049 single or twice daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c  
1050 compared to placebo plus sulfonylurea or further up-titration of the sulfonylurea. Table 8 shows  
1051 pooled data for 8 trials in which rosiglitazone added to sulfonylurea was compared to placebo  
1052 plus sulfonylurea.

1053

1054 Table 8. Glycemic Parameters in 24- to 26-Week Combination Trials of Rosiglitazone Plus  
 1055 Sulfonylurea

<b>Twice Daily Divided Dosing (5 Trials)</b>	<b>Sulfonylurea</b>	<b>Rosiglitazone 2 mg twice daily + sulfonylurea</b>	<b>Sulfonylurea</b>	<b>Rosiglitazone 4 mg twice daily + sulfonylurea</b>
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 <sup>a</sup>	—	-53 <sup>a</sup>
% 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 <sup>a</sup>	—	-1.4 <sup>a</sup>
% of patients with ≥0.7% decrease from baseline	21%	60%	23%	75%
<b>Once Daily Dosing (3 Trials)</b>	<b>Sulfonylurea</b>	<b>Rosiglitazone 4 mg once daily + sulfonylurea</b>	<b>Sulfonylurea</b>	<b>Rosiglitazone 8 mg once daily + sulfonylurea</b>
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 <sup>a</sup>	—	-66 <sup>a</sup>
% of patients with ≥30 mg/dL decrease from baseline	17%	48%	19%	55%
HbA1c (%)				
Baseline (mean)	8.6	8.8	8.9	8.9
Change from baseline	0.4	-0.5	0.1	-1.2

(mean) Difference from sulfonylurea alone (adjusted mean)	-	-0.9 <sup>a</sup>	-	-1.4 <sup>a</sup>
% of patients with $\geq 0.7\%$ decrease from baseline	11%	36%	20%	68%

1056 <sup>a</sup>  $P < 0.0001$  compared to sulfonylurea alone.

1057

1058 One of the 24- to 26-week trials included patients who were inadequately controlled on  
1059 maximal doses of glyburide and switched to 4 mg of rosiglitazone daily as monotherapy; in this  
1060 group, loss of glycemic control was demonstrated, as evidenced by increases in FPG and HbA1c.

1061 In a 2-year double-blind trial, elderly patients (aged 59 to 89 years) on half-maximal  
1062 sulfonylurea (glipizide 10 mg twice daily) were randomized to the addition of rosiglitazone  
1063 (N = 115, 4 mg once daily to 8 mg as needed) or to continued up-titration of glipizide (N = 110),  
1064 to a maximum of 20 mg twice daily. Mean baseline FPG and HbA1c were 157 mg/dL and  
1065 7.72%, respectively, for the rosiglitazone plus glipizide arm and 159 mg/dL and 7.65%,  
1066 respectively, for the glipizide up-titration arm. Loss of glycemic control (FPG  $\geq 180$  mg/dL)  
1067 occurred in a significantly lower proportion of patients (2%) on rosiglitazone plus glipizide  
1068 compared to patients in the glipizide up-titration arm (28.7%). About 78% of the patients on  
1069 combination therapy completed the 2 years of therapy while only 51% completed on glipizide  
1070 monotherapy. The effect of combination therapy on FPG and HbA1c was durable over the 2-year  
1071 trial period, with patients achieving a mean of 132 mg/dL for FPG and a mean of 6.98% for  
1072 HbA1c compared to no change on the glipizide arm.

1073

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## 1105 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1106 Each rounded triangular tablet contains rosiglitazone as the maleate and glimepiride as  
1107 follows:

1108 4 mg/1 mg – yellow, gsk debossed on one side and 4/1 on the other.

1109 4 mg/2 mg – orange, gsk debossed on one side and 4/2 on the other.

1110 4 mg/4 mg – pink, gsk debossed on one side and 4/4 on the other.

1111 8 mg/2 mg – pale pink, gsk debossed on one side and 8/2 on the other.

1112 8 mg/4 mg – red, gsk debossed on one side and 8/4 on the other.

1113

1114 4 mg/1 mg bottles of 30: NDC 0173-0841-13

1115 4 mg/2 mg bottles of 30: NDC 0173-0842-13

1116 4 mg/4 mg bottles of 30: NDC 0173-0843-13

1117 8 mg/2 mg bottles of 30: NDC 0173-0844-13

1118 8 mg/4 mg bottles of 30: NDC 0173-0845-13

1119

1120 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Dispense in a  
1121 tight, light-resistant container.

## 1122 **17 PATIENT COUNSELING INFORMATION**

1123 See Medication Guide.

### 1124 **17.1 Patient Advice**

1125 There are multiple medications available to treat type 2 diabetes. The benefits and risks  
1126 of each available diabetes medication should be taken into account when choosing a particular  
1127 diabetes medication for a given patient.

1128 Patient should fully understand the risks and benefits of AVANDARYL. AVANDARYL  
1129 should only be taken by adults with type 2 diabetes who are already taking rosiglitazone, or who  
1130 are not already taking rosiglitazone and are unable to achieve adequate glycemic control on other  
1131 diabetes medications, and, in consultation with their healthcare provider, have decided not to  
1132 take pioglitazone (ACTOS) or pioglitazone-containing medications (ACTOPLUS MET,  
1133 ACTOPLUS MET XR, DUETACT) for medical reasons. Inform patients that they must be  
1134 enrolled in the AVANDIA-Rosiglitazone Medicines Access Program in order to receive  
1135 AVANDARYL.

1136 Patients should be informed of the following:

- 1137 • AVANDARYL is not recommended in patients with symptomatic heart failure.
- 1138 • Results of a set of clinical trials suggest that treatment with AVANDARYL is associated  
1139 with an increased risk for myocardial infarction (heart attack), especially in patients taking  
1140 insulin. Clinical trials have not shown any difference between rosiglitazone and comparator  
1141 medications in overall mortality or CV-related mortality.
- 1142 • AVANDARYL is not recommended for patients who are taking insulin.
- 1143 • Management of type 2 diabetes should include diet control. Caloric restriction, weight loss,  
1144 and exercise are essential for the proper treatment of the diabetic patient because they help  
1145 improve insulin sensitivity. This is important not only in the primary treatment of type 2  
1146 diabetes, but also in maintaining the efficacy of drug therapy.
- 1147 • It is important to adhere to dietary instructions and to regularly have blood glucose and  
1148 glycosylated hemoglobin (HbA1c) tested. It can take 2 weeks to see a reduction in blood  
1149 glucose and 2 to 3 months to see the full effect of AVANDARYL.
- 1150 • The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its  
1151 development should be explained to patients and their family members.
- 1152 • Blood will be drawn to check their liver function prior to the start of therapy and periodically  
1153 thereafter per the clinical judgment of the healthcare professional. Patients with unexplained  
1154 symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should  
1155 immediately report these symptoms to their physician.
- 1156 • Patients who experience an unusually rapid increase in weight or edema or who develop  
1157 shortness of breath or other symptoms of heart failure while on AVANDARYL should  
1158 immediately report these symptoms to their physician.
- 1159 • AVANDARYL should be taken with the first meal of the day.
- 1160 • Therapy with rosiglitazone, like other thiazolidinediones, may result in ovulation in some  
1161 premenopausal anovulatory women. As a result, these patients may be at an increased risk for  
1162 pregnancy while taking AVANDARYL. Thus, adequate contraception in premenopausal  
1163 women should be recommended. This possible effect has not been specifically investigated  
1164 in clinical trials so the frequency of this occurrence is not known.
- 1165

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1175  
1176 Month 2011  
1177 AVR:XXPI

1178 **MEDICATION GUIDE**  
1179 **AVANDARYL® (ah-VAN-duh-riil)**  
1180 **(rosiglitazone maleate and glimepiride) Tablets**  
1181

1182 Read this Medication Guide carefully before you start taking AVANDARYL and each  
1183 time you get a refill. There may be new information. This information does not take  
1184 the place of talking with your doctor about your medical condition or your  
1185 treatment. If you have any questions about AVANDARYL, ask your doctor or  
1186 pharmacist.

1187  
1188 **What is the most important information I should know about AVANDARYL?**  
1189 **AVANDARYL may cause serious side effects, including:**

1190  
1191 AVANDARYL is available only through the AVANDIA-Rosiglitazone Medicines Access  
1192 Program. Both you and your doctor must be enrolled in the program so that you  
1193 can get AVANDARYL. To enroll, you must:

- 1194 • talk to your doctor,
- 1195 • understand the risks and benefits of AVANDARYL, and
- 1196 • agree to enroll in the program.

1197  
1198 **New or worse heart failure**

- 1199 • Rosiglitazone, one of the two drugs that make up AVANDARYL, can cause your  
1200 body to keep extra fluid (fluid retention), which leads to swelling (edema) and  
1201 weight gain. Extra body fluid can make some heart problems worse or lead to  
1202 heart failure. Heart failure means your heart does not pump blood well enough.
- 1203 • If you have severe heart failure, you cannot start AVANDARYL.
- 1204 • If you have heart failure with symptoms (such as shortness of breath or  
1205 swelling), even if these symptoms are not severe, AVANDARYL may not be right  
1206 for you.

1207  
1208 Call your doctor right away if you have any of the following:

- 1209 • swelling or fluid retention, especially in the ankles or legs
- 1210 • shortness of breath or trouble breathing, especially when you lie down
- 1211 • an unusually fast increase in weight
- 1212 • unusual tiredness

1213  
1214 **Myocardial Infarction (“Heart Attack”)**

1215 Rosiglitazone, one of the medicines in AVANDARYL, may raise the risk of heart  
1216 attack. The risk of having a heart attack may be higher in people who take

1217 AVANDARYL with insulin. Most people who take insulin should not also take  
1218 AVANDARYL.

1219 **Symptoms of a heart attack can include the following:**

- 1220 • chest discomfort in the center of your chest that lasts for more than a few  
1221 minutes, or that goes away or comes back  
1222 • chest discomfort that feels like uncomfortable pressure, squeezing, fullness or  
1223 pain  
1224 • pain or discomfort in your arms, back, neck, jaw or stomach  
1225 • shortness of breath with or without chest discomfort  
1226 • breaking out in a cold sweat  
1227 • nausea or vomiting  
1228 • feeling lightheaded

1229 **Call your doctor or go to the nearest hospital emergency room right away if**  
1230 **you think you are having a heart attack.**

1231  
1232 People with diabetes have a greater risk for heart problems. It is important to work  
1233 with your doctor to manage other conditions, such as high blood pressure or high  
1234 cholesterol.

1235  
1236 AVANDARYL can have other serious side effects. Be sure to read the section “What  
1237 are possible side effects of AVANDARYL?”.

1238

1239 **What is AVANDARYL?**

1240 AVANDARYL contains 2 prescription medicines to treat diabetes, rosiglitazone  
1241 maleate (AVANDIA) and glimepiride (AMARYL). AVANDARYL is used with diet and  
1242 exercise to treat certain adults with type 2 (“adult-onset” or “non-insulin  
1243 dependent”) diabetes mellitus (“high blood sugar”) who are:

- 1244 • already taking rosiglitazone or rosiglitazone-containing products  
1245 • unable to control their blood sugar on other diabetes medicines, and after  
1246 talking with their doctor have decided not to take pioglitazone (ACTOS) or  
1247 pioglitazone-containing products (ACTOPLUS MET, ACTOPLUS MET XR,  
1248 DUETACT)

1249

1250 Glimepiride can help your body release more of its own insulin. Rosiglitazone can  
1251 help your body respond better to the insulin made in your body and does not cause  
1252 your body to make more insulin. These medicines can work together to help control  
1253 your blood sugar.

1254

1255 AVANDARYL is not for people with type 1 diabetes mellitus or to treat a condition  
1256 called diabetic ketoacidosis.



1257

1258 It is not known if AVANDARYL is safe and effective in children under 18 years old.

1259

1260 **Who should not take AVANDARYL?**

1261 Many people with heart failure should not start taking AVANDARYL (see “What  
1262 should I tell my doctor before taking AVANDARYL?”).

1263

1264 **What should I tell my doctor before taking AVANDARYL?**

1265 Before starting AVANDARYL, ask your doctor about what the choices are for  
1266 diabetes medicines and what the expected benefits and possible risks are for you in  
1267 particular.

1268

1269 Before taking AVANDARYL, tell your doctor about all your medical conditions,  
1270 including if you:

- 1271 • **have heart problems or heart failure.**
- 1272 • **have type 1 (“juvenile”) diabetes or had diabetic ketoacidosis.** These  
1273 conditions should be treated with insulin and should not be treated with  
1274 AVANDARYL.
- 1275 • **have a type of diabetic eye disease called macular edema** (swelling of the  
1276 back of the eye).
- 1277 • **have liver problems.** Your doctor should do blood tests to check your liver  
1278 before you start taking AVANDARYL and during treatment as needed.
- 1279 • **had liver problems while taking REZULIN<sup>®</sup> (troglitazone), another  
1280 medicine for diabetes.**
- 1281 • **have kidney problems.** If people with kidney problems use AVANDARYL, they  
1282 may need a lower dose of the medication.
- 1283 • **have glucose 6-phosphate dehydrogenase (G6PD) deficiency.** This  
1284 condition runs in families. People with G6PD deficiency who take glimepiride  
1285 (one of the medicines in AVANDARYL) may develop hemolytic anemia (fast  
1286 breakdown of red blood cells).
- 1287 • **are pregnant or plan to become pregnant.** AVANDARYL should not be used  
1288 during pregnancy. It is not known if AVANDARYL can harm your unborn baby.  
1289 You and your doctor should talk about the best way to control your diabetes  
1290 during pregnancy. If you are a premenopausal woman (before the “change of  
1291 life”) who does not have regular monthly periods, AVANDARYL may increase  
1292 your chances of becoming pregnant. Talk to your doctor about birth control  
1293 choices while taking AVANDARYL. Tell your doctor right away if you become  
1294 pregnant while taking AVANDARYL.

1295 • **are breast-feeding or planning to breast-feed.** It is not known if  
1296 AVANDARYL passes into breast milk. You should not use AVANDARYL while  
1297 breast-feeding.

1298  
1299 Tell your doctor about all the medicines you take including prescription and non-  
1300 prescription medicines, vitamins or herbal supplements. AVANDARYL and certain  
1301 other medicines can affect each other and may lead to serious side effects including  
1302 high or low blood sugar, or heart problems. Especially tell your doctor if you take:

- 1303 • **insulin.**
- 1304 • **any medicines for high blood pressure, high cholesterol or heart failure,**  
1305 **or for prevention of heart disease or stroke.**

1306  
1307 Know the medicines you take. Keep a list of all your medicines and show it to your  
1308 doctor and pharmacist before you start a new medicine. They will tell you if it is  
1309 alright to take AVANDARYL with other medicines.

1310

#### 1311 **How should I take AVANDARYL?**

- 1312 • Take AVANDARYL exactly as prescribed. Your doctor may need to change your  
1313 dose until your blood sugar is better controlled.
- 1314 • Take AVANDARYL by mouth one time each day with your first main meal.
- 1315 • It usually takes a few days for AVANDARYL to start lowering your blood sugar. It  
1316 may take 2 to 3 months to see the full effect on your blood sugar level.
- 1317 • If you miss a dose of AVANDARYL, take it as soon as you remember unless it is  
1318 time to take your next dose. Take your next dose at the usual time. Do not take  
1319 double doses to make up for a missed dose.
- 1320 • If you take too much AVANDARYL, call your doctor or poison control center right  
1321 away.
- 1322 • Test your blood sugar regularly as your doctor tells you.
- 1323 • Your doctor should do blood tests to check your liver before you start  
1324 AVANDARYL and during treatment as needed. Your doctor should also do regular  
1325 blood sugar tests (for example, "A1c") to monitor your response to AVANDARYL.
- 1326 • Call your doctor if you get sick, get injured, get an infection, or have surgery.  
1327 AVANDARYL may not control your blood sugar levels during these times. Your  
1328 doctor may need to stop AVANDARYL for a short time and give you insulin to  
1329 control your blood sugar level.
- 1330 • Diet and exercise can help your body use its blood sugar better. It is important  
1331 to stay on your recommended diet, lose extra weight, and get regular exercise  
1332 while taking AVANDARYL.

1333

- 1334 **What are possible side effects of AVANDARYL?**
- 1335 **AVANDARYL may cause serious side effects, including:**
- 1336 • **New or worse heart failure.** See “What is the most important information I  
1337 should know about AVANDARYL?”.
  - 1338 • **Heart attack.** See “What is the most important information I should know  
1339 about AVANDARYL?”.
  - 1340 • **Swelling (edema).** AVANDARYL can cause swelling due to fluid retention. See  
1341 “What is the most important information I should know about AVANDARYL?”.
  - 1342 • **Low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness or  
1343 hunger may mean that your blood sugar is too low. This can happen if you skip  
1344 meals, drink alcohol, use another medicine that lowers blood sugar, exercise  
1345 (particularly hard or long), or if you have certain medical problems. Call your  
1346 doctor if low blood sugar levels are a problem for you.
  - 1347 • **Weight gain.** Rosiglitazone, one of the medicines in AVANDARYL, can cause  
1348 weight gain that may be due to fluid retention or extra body fat. Weight gain can  
1349 be a serious problem for people with certain conditions including heart problems.  
1350 See “What is the most important information I should know about  
1351 AVANDARYL?”.
  - 1352 • **Liver problems.** It is important for your liver to be working normally when you  
1353 take AVANDARYL. Your doctor should do blood tests to check your liver before  
1354 you start taking AVANDARYL and during treatment as needed. Call your doctor  
1355 right away if you have unexplained symptoms such as:
    - 1356 • nausea or vomiting
    - 1357 • stomach pain
    - 1358 • unusual or unexplained tiredness
    - 1359 • loss of appetite
    - 1360 • dark urine
    - 1361 • yellowing of your skin or the whites of your eyes.
  - 1362 • **Macular edema** (a diabetic eye disease with swelling in the back of the eye).  
1363 Tell your doctor right away if you have any changes in your vision. Your doctor  
1364 should check your eyes regularly. Very rarely, some people have had vision  
1365 changes due to swelling in the back of the eye while taking rosiglitazone, one of  
1366 the medicines in AVANDARYL.
  - 1367 • **Fractures (broken bones)**, usually in the hand, upper arm or foot. Talk to  
1368 your doctor for advice on how to keep your bones healthy.
  - 1369 • **Low red blood cell count (anemia).**
  - 1370 • **Ovulation** (release of egg from an ovary in women) leading to pregnancy.  
1371 Ovulation may happen in premenopausal women who do not have regular  
1372 monthly periods. This can increase the chance of pregnancy. See “What should I  
1373 tell my doctor before taking AVANDARYL?”.

1374

1375 The most common side effects with AVANDARYL include cold-like symptoms and  
1376 headache.

1377

1378 Call your doctor for medical advice about side effects. You may report side effects  
1379 to FDA at 1-800-FDA-1088.

1380

### 1381 **How should I store AVANDARYL?**

1382 • Store AVANDARYL at room temperature, 59° to 86° F (15° to 30° C). Keep  
1383 AVANDARYL in the container it comes in. Keep the container closed tightly.

1384 • Safely, throw away AVANDARYL that is out of date or no longer needed.

1385

1386 Keep AVANDARYL and all medicines out of the reach of children.

1387

### 1388 **General information about AVANDARYL**

1389 Medicines are sometimes prescribed for purposes other than those listed in a  
1390 Medication Guide. Do not use AVANDARYL for a condition for which it was not  
1391 prescribed. Do not give AVANDARYL to other people, even if they have the same  
1392 symptoms you have. It may harm them.

1393

1394 This Medication Guide summarizes important information about AVANDARYL. If you  
1395 would like more information, talk with your doctor. You can ask your doctor or  
1396 pharmacist for information about AVANDARYL that is written for healthcare  
1397 professionals. You can also find out more about AVANDARYL by calling 1-888-825-  
1398 5249.

1399

### 1400 **What are the ingredients in AVANDARYL?**

1401 Active Ingredients: Rosiglitazone maleate and glimepiride.

1402 Inactive Ingredients: Hypromellose 2910, lactose monohydrate, macrogol  
1403 (polyethylene glycol), magnesium stearate, microcrystalline cellulose, sodium  
1404 starch glycolate, titanium dioxide, triacetin, and 1 or more of the following: Yellow,  
1405 red, or black iron oxides.

1406

1407 Always check to make sure that the medicine you are taking is the correct one.

1408 AVANDARYL tablets are triangles with rounded corners and look like this:

1409 4 mg/1 mg – yellow with “gsk” on one side and “4/1” on the other.

1410 4 mg/2 mg – orange with “gsk” on one side and “4/2” on the other.

1411 4 mg/4 mg – pink with “gsk” on one side and “4/4” on the other.

1412 8 mg/2 mg – pale pink with “gsk” on one side and “8/2” on the other.

1413 8 mg/4 mg – red with “gsk” on one side and “8/4” on the other.

1414  
1415 AVANDARYL and AVANDIA are registered trademarks of GlaxoSmithKline.  
1416 The other brands listed are trademarks of their respective owners and are not  
1417 trademarks of GlaxoSmithKline. The makers of these brands are not affiliated with  
1418 and do not endorse GlaxoSmithKline or its products.

1419  
1420 **This Medication Guide has been approved by the U.S. Food and Drug**  
1421 **Administration.**

1422



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1424 GlaxoSmithKline  
1425 Research Triangle Park, NC 27709  
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1428  
1429 Month 2011  
1430 AVR: XMG