

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

AVANDIA (rosiglitazone maleate) Tablets  
Initial U.S. Approval: 1999

**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 (5.1). After initiation of AVANDIA, 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 AVANDIA must be considered.

• AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.1)

• A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with a statistically significant increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067 total patients), comparing AVANDIA 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 AVANDIA and ACTOS® (pioglitazone, another thiazolidinedione), but in a separate trial, ACTOS (when compared to placebo) did not show an increased risk of myocardial infarction or death. (5.2)

• Because of the potential increased risk of myocardial infarction, AVANDIA 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 (5.3).]

**RECENT MAJOR CHANGES**

Boxed Warning	02/2011
Indications and Usage (1)	02/2011
Dosage and Administration (2)	02/2011
Warnings and Precautions, Cardiac Failure (5.1)	02/2011
Warnings and Precautions, Major Adverse Cardiovascular Events (5.2)	02/2011
Warnings and Precautions, Rosiglitazone REMS Program (5.3)	XX/2011
Warnings and Precautions, Fractures (5.8)	02/2011

**INDICATIONS AND USAGE**

AVANDIA is a thiazolidinedione antidiabetic agent. After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of AVANDIA, this drug is indicated as an adjunct to diet and

exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are:

- already taking AVANDIA, or
- not already taking AVANDIA and are unable to achieve adequate glycemic control on other diabetes medications, and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS) for medical reasons. (1)

Other Important Limitations of Use:

- AVANDIA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. (1)
- Coadministration of AVANDIA and insulin is not recommended. (1, 5.1, 5.2)

**DOSAGE AND ADMINISTRATION**

- Start at 4 mg daily in single or divided doses; do not exceed 8 mg daily. (2)
- Dose increases should be accompanied by careful monitoring for adverse events related to fluid retention. (2)
- Do not initiate AVANDIA if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels. (2.1)

**DOSAGE FORMS AND STRENGTHS**

Pentagonal, film-coated tablets in the following strengths:

- 2 mg, 4 mg, and 8 mg (3)

**CONTRAINDICATIONS**

Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. (4)

**WARNINGS AND PRECAUTIONS**

- 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. (5.1)
- Increased risk of myocardial infarction has been observed in a meta-analysis of 52 clinical trials (incidence rate 0.4% versus 0.3%). (5.2)
- Coadministration of AVANDIA and insulin is not recommended. (1, 5.1, 5.2)
- Dose-related edema (5.4), weight gain (5.5), and anemia (5.9) may occur.
- Macular edema has been reported. (5.7)
- Increased incidence of bone fracture. (5.8)

**ADVERSE REACTIONS**

Common adverse reactions (>5%) reported in clinical trials without regard to causality were upper respiratory tract infection, injury, and headache. (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; inducers of CYP2C8 (e.g., rifampin) may decrease rosiglitazone levels. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: XX/2011

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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 (5.1)]. After initiation of AVANDIA, and after  
5 dose increases, observe patients carefully for signs and symptoms of heart failure (including  
6 excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop,  
7 the heart failure should be managed according to current standards of care. Furthermore,  
8 discontinuation or dose reduction of AVANDIA must be considered.
- 9 • AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of  
10 AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated.  
11 [See Contraindications (4) and Warnings and Precautions (5.1).]
- 12 • A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of  
13 which compared AVANDIA to placebo, showed AVANDIA to be associated with a  
14 statistically significant increased risk of myocardial infarction. Three other trials (mean  
15 duration 46 months; 14,067 total patients), comparing AVANDIA to some other approved  
16 oral antidiabetic agents or placebo, showed a statistically non-significant increased risk of  
17 myocardial infarction, and a statistically non-significant decreased risk of death. There have  
18 been no clinical trials directly comparing cardiovascular risk of AVANDIA and ACTOS<sup>®</sup>  
19 (pioglitazone, another thiazolidinedione), but in a separate trial, pioglitazone (when compared  
20 to placebo) did not show an increased risk of myocardial infarction or death. [See Warnings  
21 and Precautions (5.2).]
- 22 • Because of the potential increased risk of myocardial infarction, AVANDIA is available only  
23 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 (5.3).]

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 AVANDIA<sup>®</sup>, this drug is indicated as an adjunct to diet and  
29 exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are:

- 30 • already taking AVANDIA, or  
31 • not already taking AVANDIA and are unable to achieve adequate glycemic control on other  
32 diabetes medications and, in consultation with their healthcare provider, have decided not to  
33 take pioglitazone (ACTOS<sup>®</sup>) for medical reasons.

34 **Other Important Limitations of Use:**

- 35 • Due to its mechanism of action, AVANDIA is active only in the presence of endogenous  
36 insulin. Therefore, AVANDIA should not be used in patients with type 1 diabetes mellitus or

- 37 for the treatment of diabetic ketoacidosis.
- 38 • The coadministration of AVANDIA and insulin is not recommended [see *Warnings and*  
39 *Precautions (5.1)*].

## 40 **2 DOSAGE AND ADMINISTRATION**

41 Prior to prescribing AVANDIA, refer to *Indications and Usage (1)* for appropriate  
42 patient selection. Only prescribers enrolled in the AVANDIA-Rosiglitazone Medicines Access  
43 Program can prescribe AVANDIA [see *Warnings and Precautions (5.3)*].

44 AVANDIA may be administered at a starting dose of 4 mg either as a single daily dose or  
45 in 2 divided doses. For patients who respond inadequately following 8 to 12 weeks of treatment,  
46 as determined by reduction in fasting plasma glucose (FPG), the dose may be increased to 8 mg  
47 daily. Increases in the dose of AVANDIA should be accompanied by careful monitoring for  
48 adverse events related to fluid retention [see *Boxed Warning and Warnings and Precautions*  
49 *(5.1)*]. AVANDIA may be taken with or without food.

50 The total daily dose of AVANDIA should not exceed 8 mg.

51 Patients receiving AVANDIA in combination with other hypoglycemic agents may be at  
52 risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

### 53 **2.1 Specific Patient Populations**

54 Renal Impairment: No dosage adjustment is necessary when AVANDIA is used as  
55 monotherapy in patients with renal impairment. Since metformin is contraindicated in such  
56 patients, concomitant administration of metformin and AVANDIA is also contraindicated in  
57 patients with renal impairment.

58 Hepatic Impairment: Liver enzymes should be measured prior to initiating treatment  
59 with AVANDIA. Therapy with AVANDIA should not be initiated if the patient exhibits clinical  
60 evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit  
61 of normal at start of therapy). After initiation of AVANDIA, liver enzymes should be monitored  
62 periodically per the clinical judgment of the healthcare professional. [See *Warnings and*  
63 *Precautions (5.6) and Clinical Pharmacology (12.3)*.]

64 Pediatric: Data are insufficient to recommend pediatric use of AVANDIA [see *Use in*  
65 *Specific Populations (8.4)*].

## 66 **3 DOSAGE FORMS AND STRENGTHS**

67 Pentagonal film-coated TILTAB<sup>®</sup> tablet contains rosiglitazone as the maleate as follows:

- 68 • 2 mg - pink, debossed with SB on one side and 2 on the other  
69 • 4 mg - orange, debossed with SB on one side and 4 on the other  
70 • 8 mg - red-brown, debossed with SB on one side and 8 on the other

## 71 **4 CONTRAINDICATIONS**

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

74 **5 WARNINGS AND PRECAUTIONS**

75 **5.1 Cardiac Failure**

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

81 Patients with congestive heart failure (CHF) NYHA Class I and II treated with  
82 AVANDIA have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-  
83 controlled echocardiographic trial was conducted in 224 patients with type 2 diabetes mellitus  
84 and NYHA Class I or II CHF (ejection fraction  $\leq 45\%$ ) on background antidiabetic and CHF  
85 therapy. An independent committee conducted a blinded evaluation of fluid-related events  
86 (including congestive heart failure) and cardiovascular hospitalizations according to predefined  
87 criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were  
88 reported by investigators. Although no treatment difference in change from baseline of ejection  
89 fractions was observed, more cardiovascular adverse events were observed following treatment  
90 with AVANDIA compared to placebo during the 52-week trial. (See Table 1.)  
91

92 Table 1. Emergent Cardiovascular Adverse Events in Patients With Congestive Heart  
93 Failure (NYHA Class I and II) Treated With AVANDIA or Placebo (in Addition to  
94 Background Antidiabetic and CHF Therapy)

<b>Events</b>	<b>AVANDIA</b>	<b>Placebo</b>
	N = 110 n (%)	N = 114 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%)

95 <sup>a</sup> Includes hospitalization for any cardiovascular reason.  
96

97 Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is  
98 contraindicated. AVANDIA is not recommended in patients with symptomatic heart failure. [See  
99 *Boxed Warning.*]

100 Patients experiencing acute coronary syndromes have not been studied in controlled  
101 clinical trials. In view of the potential for development of heart failure in patients having an acute  
102 coronary event, initiation of AVANDIA is not recommended for patients experiencing an acute  
103 coronary event, and discontinuation of AVANDIA during this acute phase should be considered.

104 Patients with NYHA Class III and IV cardiac status (with or without CHF) have not been  
105 studied in controlled clinical trials. AVANDIA is not recommended in patients with NYHA  
106 Class III and IV cardiac status.

107 Congestive Heart Failure During Coadministration of AVANDIA With Insulin: In  
108 trials in which AVANDIA was added to insulin, AVANDIA increased the risk of congestive  
109 heart failure. Coadministration of AVANDIA and insulin is not recommended. [See *Indications*  
110 *and Usage (1) and Warnings and Precautions (5.2).*]

111 In 7 controlled, randomized, double-blind trials which had durations from 16 to 26 weeks

112 and which were included in a meta-analysis<sup>1</sup> [see *Warnings and Precautions* (5.2)], patients with  
113 type 2 diabetes mellitus were randomized to coadministration of AVANDIA and insulin  
114 (N = 1,018) or insulin (N = 815). In these 7 trials, AVANDIA was added to insulin. These trials  
115 included patients with long-standing diabetes (median duration of 12 years) and a high  
116 prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy,  
117 ischemic heart disease, vascular disease, and congestive heart failure. The total number of  
118 patients with emergent congestive heart failure was 23 (2.3%) and 8 (1.0%) in the AVANDIA  
119 plus insulin and insulin groups, respectively.

120 **Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing**  
121 **AVANDIA to ACTOS:** Three observational studies<sup>2-4</sup> in elderly diabetic patients (age 65 years  
122 and older) found that AVANDIA statistically significantly increased the risk of hospitalized  
123 heart failure compared to use of ACTOS. One other observational study<sup>5</sup> in patients with a mean  
124 age of 54 years, which also included an analysis in a subpopulation of patients >65 years of age,  
125 found no statistically significant increase in emergency department visits or hospitalization for  
126 heart failure in patients treated with AVANDIA compared to ACTOS in the older subgroup.

127 **5.2 Major Adverse Cardiovascular Events**

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

130 **Meta-Analysis of Major Adverse Cardiovascular Events in a Group of 52 Clinical**  
131 **Trials:** A meta-analysis was conducted retrospectively to assess cardiovascular adverse events  
132 reported across 52 double-blind, randomized, controlled clinical trials (mean duration 6  
133 months).<sup>1</sup> These trials had been conducted to assess glucose-lowering efficacy in type 2 diabetes.  
134 Prospectively planned adjudication of cardiovascular events did not occur in most of the trials.  
135 Some trials were placebo-controlled and some used active oral antidiabetic drugs as controls.  
136 Placebo-controlled trials included monotherapy trials (monotherapy with AVANDIA versus  
137 placebo monotherapy) and add-on trials (AVANDIA or placebo, added to sulfonylurea,  
138 metformin, or insulin). Active control trials included monotherapy trials (monotherapy with  
139 AVANDIA versus sulfonylurea or metformin monotherapy) and add-on trials (AVANDIA plus  
140 sulfonylurea or AVANDIA plus metformin, versus sulfonylurea plus metformin). A total of  
141 16,995 patients were included (10,039 in treatment groups containing AVANDIA, 6,956 in  
142 comparator groups), with 5,167 patient-years of exposure to AVANDIA and 3,637 patient-years  
143 of exposure to comparator. Cardiovascular events occurred more frequently for patients who  
144 received AVANDIA than for patients who received comparators (see Table 2).  
145

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

Event <sup>a</sup>	AVANDIA (Rosiglitazone) (N = 10,039) n (%)	Comparator (N = 6,956) n (%)
MACE (a composite of myocardial	70 (0.7)	39 (0.6)

infarction, cardiovascular death, or stroke)		
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)

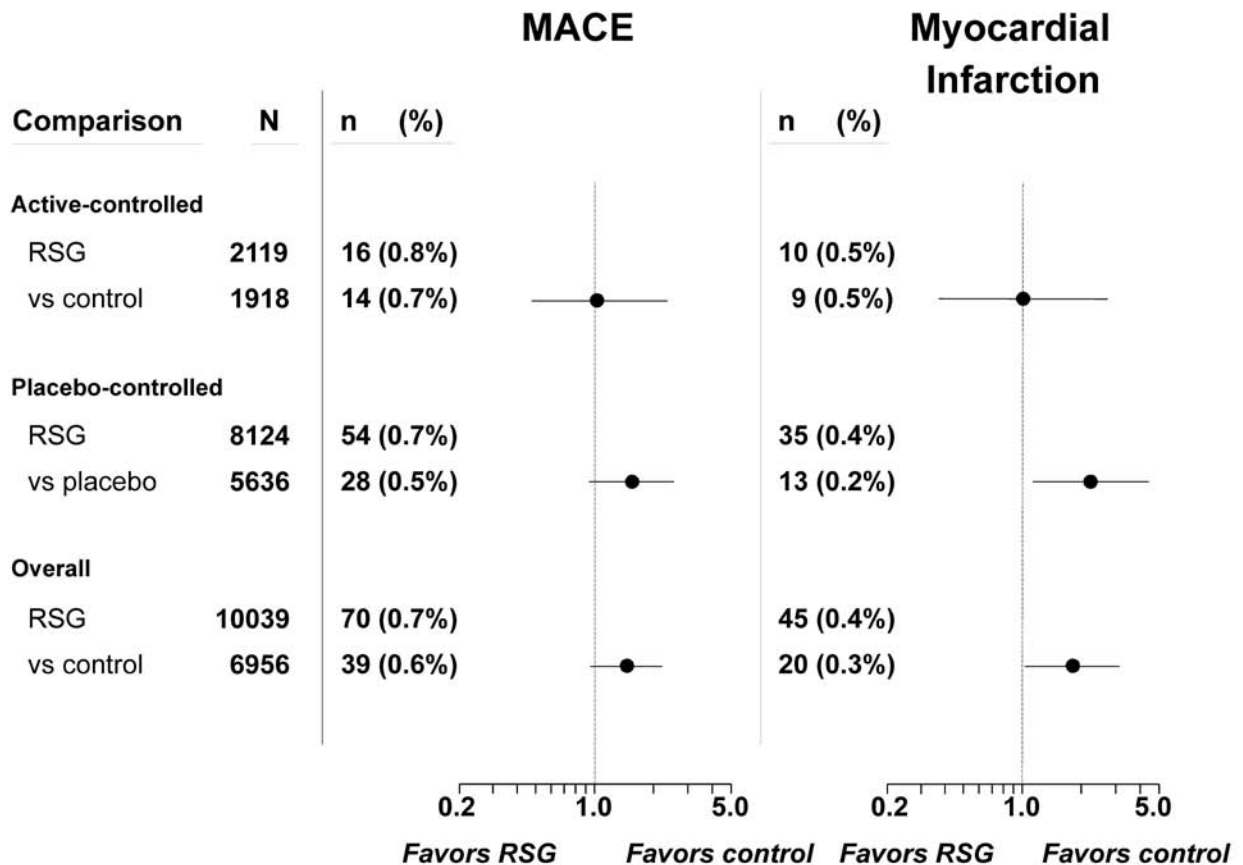
147 <sup>a</sup> Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial  
148 infarction would be counted in 4 event categories (myocardial infarction; myocardial  
149 infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).

150

151 In this analysis, a statistically significant increased risk of myocardial infarction with  
152 AVANDIA versus pooled comparators was observed. Analyses were performed using a  
153 composite of major adverse cardiovascular events (myocardial infarction, stroke, and  
154 cardiovascular death), referred to hereafter as MACE. AVANDIA had a statistically non-  
155 significant increased risk of MACE compared to the pooled comparators. A statistically  
156 significant increased risk of myocardial infarction and statistically non-significant increased risk  
157 of MACE with AVANDIA was observed in the placebo-controlled trials. In the active-controlled  
158 trials, there was no increased risk of myocardial infarction or MACE. (See Figure 1 and Table 3.)

159

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



RSG = rosiglitazone

162  
163  
164  
165

**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%)	

166 RSG = AVANDIA (rosiglitazone)

167  
168  
169

Of the placebo-controlled trials in the meta-analysis, 7 trials had patients randomized to AVANDIA plus insulin or insulin. There were more patients in the AVANDIA plus insulin

170 group compared to the insulin group with myocardial infarctions, MACE, cardiovascular deaths,  
171 and all-cause deaths (see Table 4). The total number of patients with stroke was 5 (0.5%) and 4  
172 (0.5%) in the AVANDIA plus insulin and insulin groups, respectively. The use of AVANDIA in  
173 combination with insulin may increase the risk of myocardial infarction.  
174

175 **Table 4. Occurrence of Cardiovascular Events for AVANDIA in Combination With Insulin**  
176 **in a Meta-Analysis of 52 Clinical Trials**

Event <sup>a</sup>	AVANDIA (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)

177 ND = not defined

178 <sup>a</sup> Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial  
179 infarction would be counted in 4 event categories (myocardial infarction; myocardial  
180 infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).  
181

182 **Myocardial Infarction Events in Large, Long-Term, Prospective, Randomized,**  
183 **Controlled Trials of AVANDIA:** Data from 3 large, long-term, prospective, randomized,  
184 controlled clinical trials of AVANDIA were assessed separately from the meta-analysis.<sup>6-8</sup> These  
185 3 trials included a total of 14,067 patients (treatment groups containing AVANDIA N = 6,311;  
186 comparator groups N = 7,756), with patient-year exposure of 24,534 patient-years for  
187 AVANDIA and 28,882 patient-years for comparator. Patient populations in the trials included  
188 patients with impaired glucose tolerance, patients with type 2 diabetes who were initiating oral  
189 agent monotherapy, and patients with type 2 diabetes who had failed monotherapy and were  
190 initiating dual oral agent therapy. Duration of follow-up exceeded 3 years in each trial.

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

193 In a long-term, randomized, placebo-controlled, 2x2 factorial trial intended to evaluate  
194 AVANDIA, and separately ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on  
195 progression to overt diabetes in 5,269 subjects with glucose intolerance, the incidence of  
196 myocardial infarction was higher in the subset of subjects who received AVANDIA in  
197 combination with ramipril than among subjects who received ramipril alone but not in the subset  
198 of subjects who received AVANDIA alone compared to placebo.<sup>6</sup> The higher incidence of  
199 myocardial infarction among subjects who received AVANDIA in combination with ramipril

200 was not confirmed in the two other large (total N = 8,798) long-term, randomized, active-  
201 controlled clinical trials conducted in patients with type 2 diabetes, in which 30% and 40% of  
202 patients in the two trials reported angiotensin-converting enzyme inhibitor use at baseline.<sup>7,8</sup>

203 There have been no adequately designed clinical trials directly comparing AVANDIA to  
204 ACTOS (pioglitazone) on cardiovascular risks. However, in a long-term, randomized, placebo-  
205 controlled cardiovascular outcomes trial comparing ACTOS (pioglitazone) to placebo in patients  
206 with type 2 diabetes mellitus and prior macrovascular disease, ACTOS (pioglitazone) was not  
207 associated with an increased risk of myocardial infarction or total mortality.<sup>9</sup>

208 The increased risk of myocardial infarction observed in the meta-analysis and large, long-  
209 term controlled clinical trials, and the increased risk of MACE observed in the meta-analysis  
210 described above, have not translated into a consistent finding of excess mortality from controlled  
211 clinical trials or observational studies. Clinical trials have not shown any difference between  
212 AVANDIA and comparator medications in overall mortality or CV-related mortality.

213 Mortality in Observational Studies of AVANDIA Compared to ACTOS: Three  
214 observational studies in elderly diabetic patients (age 65 years and older) found that AVANDIA  
215 statistically significantly increased the risk of all-cause mortality compared to use of ACTOS.<sup>2-4</sup>  
216 One observational study<sup>5</sup> in patients with a mean age of 54 years found no difference in all-cause  
217 mortality between patients treated with AVANDIA compared to ACTOS and reported similar  
218 results in the subpopulation of patients >65 years of age. One additional small, prospective,  
219 observational study<sup>10</sup> found no statistically significant differences for CV mortality and all-cause  
220 mortality in patients treated with AVANDIA compared to ACTOS.

### 221 **5.3 Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program**

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

### 231 **5.4 Edema**

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

235 Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can  
236 exacerbate or lead to congestive heart failure, AVANDIA should be used with caution in patients  
237 at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure  
238 [*see Boxed Warning, Warnings and Precautions (5.1), and Patient Counseling Information*  
239 (17)].

240 In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was  
241 reported in patients treated with AVANDIA, and may be dose related. Patients with ongoing  
242 edema were more likely to have adverse events associated with edema if started on combination  
243 therapy with insulin and AVANDIA [see Adverse Reactions (6.1)].

244 **5.5 Weight Gain**

245 Dose-related weight gain was seen with AVANDIA alone and in combination with other  
246 hypoglycemic agents (Table 5). The mechanism of weight gain is unclear but probably involves  
247 a combination of fluid retention and fat accumulation.

248 In postmarketing experience, there have been reports of unusually rapid increases in  
249 weight and increases in excess of that generally observed in clinical trials. Patients who  
250 experience such increases should be assessed for fluid accumulation and volume-related events  
251 such as excessive edema and congestive heart failure [see Boxed Warning].

252  
253 Table 5. Weight Changes (kg) From Baseline at Endpoint During Clinical Trials

		Control Group		AVANDIA 4 mg	AVANDIA 8 mg
Monotherapy	Duration		Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)
	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>					
Sulfonylurea	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
Metformin	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
Insulin	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
Sulfonylurea + metformin	26 weeks	sulfonylurea + metformin	0.2 (-1.2, 1.6) N = 272	2.5 (0.8, 4.6) N = 275	4.5 (2.4, 7.3) N = 276

254  
255 In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed  
256 with type 2 diabetes not previously treated with antidiabetic medication [see Clinical Studies  
257 (14.1)], the median weight change (25<sup>th</sup>, 75<sup>th</sup> percentiles) from baseline at 4 years was 3.5 kg  
258 (0.0, 8.1) for AVANDIA, 2.0 kg (-1.0, 4.8) for glyburide, and -2.4 kg (-5.4, 0.5) for metformin.

259 In a 24-week trial in pediatric patients aged 10 to 17 years treated with AVANDIA 4 to  
260 8 mg daily, a median weight gain of 2.8 kg (25<sup>th</sup>, 75<sup>th</sup> percentiles: 0.0, 5.8) was reported.

261 **5.6 Hepatic Effects**

262 Liver enzymes should be measured prior to the initiation of therapy with AVANDIA in  
263 all patients and periodically thereafter per the clinical judgment of the healthcare professional.  
264 Therapy with AVANDIA should not be initiated in patients with increased baseline liver enzyme  
265 levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes (ALT  
266 levels ≤2.5X upper limit of normal) at baseline or during therapy with AVANDIA should be  
267 evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of,  
268 therapy with AVANDIA in patients with mild liver enzyme elevations should proceed with  
269 caution and include close clinical follow-up, including liver enzyme monitoring, to determine if  
270 the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X the  
271 upper limit of normal in patients on therapy with AVANDIA, liver enzyme levels should be  
272 rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with  
273 AVANDIA should be discontinued.

274 If any patient develops symptoms suggesting hepatic dysfunction, which may include  
275 unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver  
276 enzymes should be checked. The decision whether to continue the patient on therapy with  
277 AVANDIA should be guided by clinical judgment pending laboratory evaluations. If jaundice is  
278 observed, drug therapy should be discontinued. [See Adverse Reactions (6.2, 6.3).]

279 **5.7 Macular Edema**

280 Macular edema has been reported in postmarketing experience in some diabetic patients  
281 who were taking AVANDIA or another thiazolidinedione. Some patients presented with blurred  
282 vision or decreased visual acuity, but some patients appear to have been diagnosed on routine  
283 ophthalmologic examination. Most patients had peripheral edema at the time macular edema was  
284 diagnosed. Some patients had improvement in their macular edema after discontinuation of their  
285 thiazolidinedione. Patients with diabetes should have regular eye exams by an ophthalmologist,  
286 per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who  
287 reports any kind of visual symptom should be promptly referred to an ophthalmologist,  
288 regardless of the patient's underlying medications or other physical findings. [See Adverse  
289 Reactions (6.1).]

290 **5.8 Fractures**

291 In a 4- to 6-year comparative trial (ADOPT) of glycemic control with monotherapy in  
292 drug-naïve patients recently diagnosed with type 2 diabetes mellitus, an increased incidence of  
293 bone fracture was noted in female patients taking AVANDIA. Over the 4- to 6-year period, the  
294 incidence of bone fracture in females was 9.3% (60/645) for AVANDIA versus 3.5% (21/605)  
295 for glyburide and 5.1% (30/590) for metformin. This increased incidence was noted after the first  
296 year of treatment and persisted during the course of the trial. The majority of the fractures in the  
297 women who received AVANDIA occurred in the upper arm, hand, and foot. These sites of  
298 fracture are different from those usually associated with postmenopausal osteoporosis (e.g., hip  
299 or spine). Other trials suggest that this risk may also apply to men, although the risk of fracture  
300 among women appears higher than that among men. The risk of fracture should be considered in

301 the care of patients treated with AVANDIA, and attention given to assessing and maintaining  
302 bone health according to current standards of care.

### 303 **5.9 Hematologic Effects**

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

### 307 **5.10 Diabetes and Blood Glucose Control**

308 Patients receiving AVANDIA in combination with other hypoglycemic agents may be at  
309 risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

310 Periodic fasting blood glucose and HbA1c measurements should be performed to monitor  
311 therapeutic response.

### 312 **5.11 Ovulation**

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

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

## 322 **6 ADVERSE REACTIONS**

### 323 **6.1 Clinical Trial Experience**

324 Adult: In clinical trials, approximately 9,900 patients with type 2 diabetes have been  
325 treated with AVANDIA.

326 *Short-Term Trials of AVANDIA as Monotherapy and in Combination With Other*  
327 *Hypoglycemic Agents*: The incidence and types of adverse events reported in short-term  
328 clinical trials of AVANDIA as monotherapy are shown in Table 6.  
329

330 Table 6. Adverse Events (≥5% in Any Treatment Group) Reported by Patients in Short-  
331 Term<sup>a</sup> Double-Blind Clinical Trials With AVANDIA as Monotherapy

Preferred Term	AVANDIA Monotherapy	Placebo	Metformin	Sulfonylureas <sup>b</sup>
	N = 2,526	N = 601	N = 225	N = 626
	%	%	%	%
Upper respiratory tract infection	9.9	8.7	8.9	7.3
Injury	7.6	4.3	7.6	6.1
Headache	5.9	5.0	8.9	5.4
Back pain	4.0	3.8	4.0	5.0
Hyperglycemia	3.9	5.7	4.4	8.1
Fatigue	3.6	5.0	4.0	1.9
Sinusitis	3.2	4.5	5.3	3.0
Diarrhea	2.3	3.3	15.6	3.0
Hypoglycemia	0.6	0.2	1.3	5.9

332 <sup>a</sup> Short-term trials ranged from 8 weeks to 1 year.

333 <sup>b</sup> Includes patients receiving glyburide (N = 514), gliclazide (N = 91), or glipizide (N = 21).  
334

335 Overall, the types of adverse reactions without regard to causality reported when  
336 AVANDIA was used in combination with a sulfonylurea or metformin were similar to those  
337 during monotherapy with AVANDIA.

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

341 In double-blind trials, anemia was reported in 1.9% of patients receiving AVANDIA as  
342 monotherapy compared to 0.7% on placebo, 0.6% on sulfonylureas, and 2.2% on metformin.  
343 Reports of anemia were greater in patients treated with a combination of AVANDIA and  
344 metformin (7.1%) and with a combination of AVANDIA and a sulfonylurea plus metformin  
345 (6.7%) compared to monotherapy with AVANDIA or in combination with a sulfonylurea  
346 (2.3%). Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin  
347 combination clinical trials may have contributed to the higher reporting rate of anemia in these  
348 trials [*see Adverse Reactions (6.2)*].

349 In clinical trials, edema was reported in 4.8% of patients receiving AVANDIA as  
350 monotherapy compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. The  
351 reporting rate of edema was higher for AVANDIA 8 mg in sulfonylurea combinations (12.4%)  
352 compared to other combinations, with the exception of insulin. Edema was reported in 14.7% of  
353 patients receiving AVANDIA in the insulin combination trials compared to 5.4% on insulin  
354 alone. Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1%  
355 for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with AVANDIA [*see*

356 *Boxed Warning and Warnings and Precautions (5.1)*]. The use of AVANDIA in combination  
357 with insulin may increase the risk of myocardial infarction [*see Warnings and Precautions*  
358 (5.2)].

359 In controlled combination therapy trials with sulfonylureas, mild to moderate  
360 hypoglycemic symptoms, which appear to be dose related, were reported. Few patients were  
361 withdrawn for hypoglycemia (<1%) and few episodes of hypoglycemia were considered to be  
362 severe (<1%). Hypoglycemia was the most frequently reported adverse event in the fixed-dose  
363 insulin combination trials, although few patients withdrew for hypoglycemia (4 of 408 for  
364 AVANDIA plus insulin and 1 of 203 for insulin alone). Rates of hypoglycemia, confirmed by  
365 capillary blood glucose concentration ≤50 mg/dL, were 6% for insulin alone and 12% (4 mg) and  
366 14% (8 mg) for insulin in combination with AVANDIA. [*See Warnings and Precautions (5.10).*]

367 **Long-Term Trial of AVANDIA as Monotherapy:** A 4- to 6-year trial (ADOPT)  
368 compared the use of AVANDIA (n = 1,456), glyburide (n = 1,441), and metformin (n = 1,454)  
369 as monotherapy in patients recently diagnosed with type 2 diabetes who were not previously  
370 treated with antidiabetic medication. Table 7 presents adverse reactions without regard to  
371 causality; rates are expressed per 100 patient-years (PY) exposure to account for the differences  
372 in exposure to trial medication across the 3 treatment groups.

373 In ADOPT, fractures were reported in a greater number of women treated with  
374 AVANDIA (9.3%, 2.7/100 patient-years) compared to glyburide (3.5%, 1.3/100 patient-years) or  
375 metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who  
376 received rosiglitazone were reported in the upper arm, hand, and foot. [*See Warnings and*  
377 *Precautions (5.8).*] The observed incidence of fractures for male patients was similar among the  
378 3 treatment groups.

379  
380 Table 7. On-Therapy Adverse Events (≥5 Events/100 Patient-Years [PY]) in Any  
381 Treatment Group Reported in a 4- to 6-Year Clinical Trial of AVANDIA as Monotherapy  
382 (ADOPT)

	<b>AVANDIA</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

383  
384 **Pediatric:** AVANDIA has been evaluated for safety in a single, active-controlled trial of  
385 pediatric patients with type 2 diabetes in which 99 were treated with AVANDIA and 101 were

386 treated with metformin. The most common adverse reactions (>10%) without regard to causality  
387 for either AVANDIA or metformin were headache (17% versus 14%), nausea (4% versus 11%),  
388 nasopharyngitis (3% versus 12%), and diarrhea (1% versus 13%). In this trial, one case of  
389 diabetic ketoacidosis was reported in the metformin group. In addition, there were 3 patients in  
390 the rosiglitazone group who had FPG of ~300 mg/dL, 2+ ketonuria, and an elevated anion gap.

## 391 **6.2 Laboratory Abnormalities**

392 Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a dose-related  
393 fashion in adult patients treated with AVANDIA (mean decreases in individual trials as much as  
394 1.0 g/dL hemoglobin and as much as 3.3% hematocrit). The changes occurred primarily during  
395 the first 3 months following initiation of therapy with AVANDIA or following a dose increase in  
396 AVANDIA. The time course and magnitude of decreases were similar in patients treated with a  
397 combination of AVANDIA and other hypoglycemic agents or monotherapy with AVANDIA.  
398 Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin  
399 combination trials and may have contributed to the higher reporting rate of anemia. In a single  
400 trial in pediatric patients, decreases in hemoglobin and hematocrit (mean decreases of 0.29 g/dL  
401 and 0.95%, respectively) were reported. Small decreases in hemoglobin and hematocrit have also  
402 been reported in pediatric patients treated with AVANDIA. White blood cell counts also  
403 decreased slightly in adult patients treated with AVANDIA. Decreases in hematologic  
404 parameters may be related to increased plasma volume observed with treatment with  
405 AVANDIA.

406 Lipids: Changes in serum lipids have been observed following treatment with  
407 AVANDIA in adults [*see Clinical Pharmacology (12.2)*]. Small changes in serum lipid  
408 parameters were reported in children treated with AVANDIA for 24 weeks.

409 Serum Transaminase Levels: In pre-approval clinical trials in 4,598 patients treated  
410 with AVANDIA (3,600 patient-years of exposure) and in a long-term 4- to 6-year trial in 1,456  
411 patients treated with AVANDIA (4,954 patient-years exposure), there was no evidence of  
412 drug-induced hepatotoxicity.

413 In pre-approval controlled trials, 0.2% of patients treated with AVANDIA had elevations  
414 in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active  
415 comparators. The ALT elevations in patients treated with AVANDIA were reversible.  
416 Hyperbilirubinemia was found in 0.3% of patients treated with AVANDIA compared with 0.9%  
417 treated with placebo and 1% in patients treated with active comparators. In pre-approval clinical  
418 trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. [*See*  
419 *Warnings and Precautions (5.6).*]

420 In the 4- to 6-year ADOPT trial, patients treated with AVANDIA (4,954 patient-years  
421 exposure), glyburide (4,244 patient-years exposure), or metformin (4,906 patient-years  
422 exposure), as monotherapy, had the same rate of ALT increase to >3X upper limit of normal  
423 (0.3 per 100 patient-years exposure).

## 424 **6.3 Postmarketing Experience**

425 In addition to adverse reactions reported from clinical trials, the events described below

426 have been identified during post-approval use of AVANDIA. Because these events are reported  
427 voluntarily from a population of unknown size, it is not possible to reliably estimate their  
428 frequency or to always establish a causal relationship to drug exposure.

429 In patients receiving thiazolidinedione therapy, serious adverse events with or without a  
430 fatal outcome, potentially related to volume expansion (e.g., congestive heart failure, pulmonary  
431 edema, and pleural effusions) have been reported [*see Boxed Warning and Warnings and*  
432 *Precautions (5.1)*].

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

436 There are postmarketing reports with AVANDIA of rash, pruritus, urticaria, angioedema,  
437 anaphylactic reaction, Stevens-Johnson syndrome, and new onset or worsening diabetic macular  
438 edema with decreased visual acuity [*see Warnings and Precautions (5.7)*].

## 439 **7 DRUG INTERACTIONS**

### 440 **7.1 CYP2C8 Inhibitors and Inducers**

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

## 446 **8 USE IN SPECIFIC POPULATIONS**

### 447 **8.1 Pregnancy**

448 Pregnancy Category C.

449 All pregnancies have a background risk of birth defects, loss, or other adverse outcome  
450 regardless of drug exposure. This background risk is increased in pregnancies complicated by  
451 hyperglycemia and may be decreased with good metabolic control. It is essential for patients  
452 with diabetes or history of gestational diabetes to maintain good metabolic control before  
453 conception and throughout pregnancy. Careful monitoring of glucose control is essential in such  
454 patients. Most experts recommend that insulin monotherapy be used during pregnancy to  
455 maintain blood glucose levels as close to normal as possible.

456 Human Data: Rosiglitazone has been reported to cross the human placenta and be  
457 detectable in fetal tissue. The clinical significance of these findings is unknown. There are no  
458 adequate and well-controlled trials in pregnant women. AVANDIA should not be used during  
459 pregnancy.

460 Animal Studies: There was no effect on implantation or the embryo with rosiglitazone  
461 treatment during early pregnancy in rats, but treatment during mid-late gestation was associated  
462 with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed  
463 at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human  
464 AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused

465 placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation  
466 reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible  
467 after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was  
468 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately  
469 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced  
470 the number of uterine implantations and live offspring when juvenile female rats were treated at  
471 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human  
472 AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day  
473 (approximately 4 times human AUC at the maximum recommended daily dose). There was no  
474 effect on pre- or post-natal survival or growth.

## 475 **8.2 Labor and Delivery**

476 The effect of rosiglitazone on labor and delivery in humans is not known.

## 477 **8.3 Nursing Mothers**

478 Drug-related material was detected in milk from lactating rats. It is not known whether  
479 AVANDIA is excreted in human milk. Because many drugs are excreted in human milk,  
480 AVANDIA should not be administered to a nursing woman.

## 481 **8.4 Pediatric Use**

482 After placebo run-in including diet counseling, children with type 2 diabetes mellitus,  
483 aged 10 to 17 years and with a baseline mean body mass index (BMI) of 33 kg/m<sup>2</sup>, were  
484 randomized to treatment with 2 mg twice daily of AVANDIA (n = 99) or 500 mg twice daily of  
485 metformin (n = 101) in a 24-week, double-blind clinical trial. As expected, FPG decreased in  
486 patients naïve to diabetes medication (n = 104) and increased in patients withdrawn from prior  
487 medication (usually metformin) (n = 90) during the run-in period. After at least 8 weeks of  
488 treatment, 49% of patients treated with AVANDIA and 55% of metformin-treated patients had  
489 their dose doubled if FPG >126 mg/dL. For the overall intent-to-treat population, at week 24, the  
490 mean change from baseline in HbA1c was -0.14% with AVANDIA and -0.49% with metformin.  
491 There was an insufficient number of patients in this trial to establish statistically whether these  
492 observed mean treatment effects were similar or different. Treatment effects differed for patients  
493 naïve to therapy with antidiabetic drugs and for patients previously treated with antidiabetic  
494 therapy (Table 8).

495

496 Table 8. Week 24 FPG and HbA1c Change From Baseline Last-Observation-Carried  
497 Forward in Children With Baseline HbA1c >6.5%

	Naïve Patients		Previously-Treated Patients	
	Metformin	Rosiglitazone	Metformin	Rosiglitazone
	N = 40	N = 45	N = 43	N = 32
<b>FPG (mg/dL)</b>				
Baseline (mean)	170	165	221	205
Change from baseline (mean)	-21	-11	-33	-5
Adjusted treatment difference <sup>a</sup> (rosiglitazone–metformin) <sup>b</sup> (95% CI)		8 (-15, 30)		21 (-9, 51)
% of patients with ≥30 mg/dL decrease from baseline	43%	27%	44%	28%
<b>HbA1c (%)</b>				
Baseline (mean)	8.3	8.2	8.8	8.5
Change from baseline (mean)	-0.7	-0.5	-0.4	0.1
Adjusted treatment difference <sup>a</sup> (rosiglitazone–metformin) <sup>b</sup> (95% CI)		0.2 (-0.6, 0.9)		0.5 (-0.2, 1.3)
% of patients with ≥0.7% decrease from baseline	63%	52%	54%	31%

498 <sup>a</sup> Change from baseline means are least squares means adjusting for baseline HbA1c, gender,  
499 and region.

500 <sup>b</sup> Positive values for the difference favor metformin.

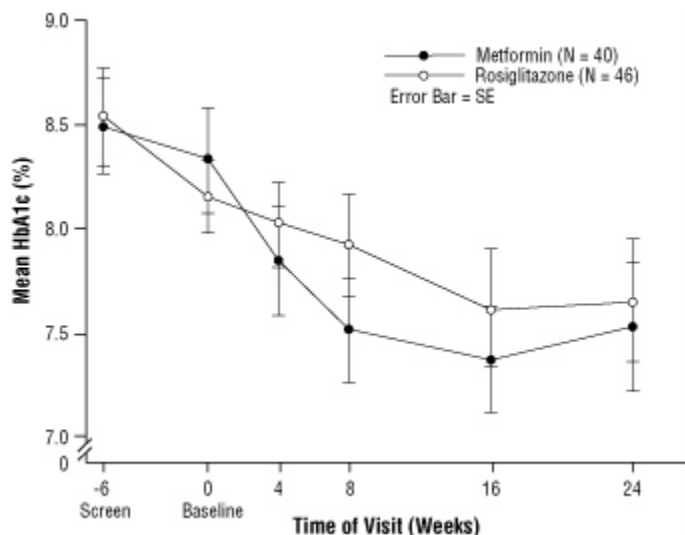
501

502 Treatment differences depended on baseline BMI or weight such that the effects of  
503 AVANDIA and metformin appeared more closely comparable among heavier patients. The  
504 median weight gain was 2.8 kg with rosiglitazone and 0.2 kg with metformin [see *Warnings and*  
505 *Precautions (5.5)*]. Fifty-four percent of patients treated with rosiglitazone and 32% of patients  
506 treated with metformin gained ≥2 kg, and 33% of patients treated with rosiglitazone and 7% of  
507 patients treated with metformin gained ≥5 kg on trial.

508 Adverse events observed in this trial are described in *Adverse Reactions (6.1)*.

509

510 Figure 2. Mean HbA1c Over Time in a 24-Week Trial of AVANDIA and Metformin in  
511 Pediatric Patients — Drug-Naïve Subgroup



512  
513

## 514 8.5 Geriatric Use

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

## 520 10 OVERDOSAGE

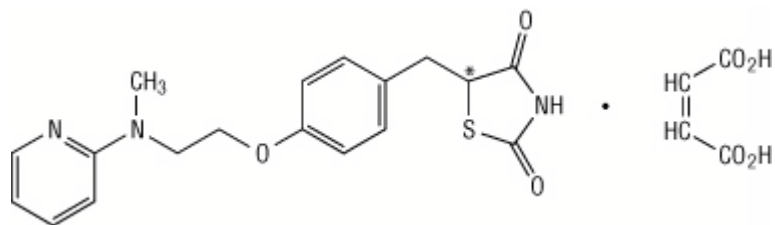
521 Limited data are available with regard to overdosage in humans. In clinical trials in  
522 volunteers, AVANDIA has been administered at single oral doses of up to 20 mg and was  
523 well-tolerated. In the event of an overdose, appropriate supportive treatment should be initiated  
524 as dictated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

## 525 11 DESCRIPTION

526 AVANDIA (rosiglitazone maleate) is an oral antidiabetic agent which acts primarily by  
527 increasing insulin sensitivity. AVANDIA improves glycemic control while reducing circulating  
528 insulin levels.

529 Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the  
530 biguanides, or the alpha-glucosidase inhibitors.

531 Chemically, rosiglitazone maleate is ( $\pm$ )-5-[[4-[2-(methyl-2-  
532 pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (*Z*)-2-butenedioate (1:1) with a  
533 molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is  
534 present as a racemate. Due to rapid interconversion, the enantiomers are functionally  
535 indistinguishable. The structural formula of rosiglitazone maleate is:



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The molecular formula is  $C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$ . Rosiglitazone maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pKa values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

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Each pentagonal film-coated TILTAB tablet contains rosiglitazone maleate equivalent to rosiglitazone, 2 mg, 4 mg, or 8 mg, for oral administration. Inactive ingredients are: Hypromellose 2910, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin, and 1 or more of the following: Synthetic red and yellow iron oxides and talc.

546

## 12 CLINICAL PHARMACOLOGY

547

### 12.1 Mechanism of Action

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

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

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

566

### 12.2 Pharmacodynamics

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Patients with lipid abnormalities were not excluded from clinical trials of AVANDIA. In all 26-week controlled trials, across the recommended dose range, AVANDIA as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids. These changes were statistically significantly different from placebo or glyburide controls

571 (Table 9).

572 Increases in LDL occurred primarily during the first 1 to 2 months of therapy with  
573 AVANDIA and LDL levels remained elevated above baseline throughout the trials. In contrast,  
574 HDL continued to rise over time. As a result, the LDL/HDL ratio peaked after 2 months of  
575 therapy and then appeared to decrease over time. Because of the temporal nature of lipid  
576 changes, the 52-week glyburide-controlled trial is most pertinent to assess long-term effects on  
577 lipids. At baseline, week 26, and week 52, mean LDL/HDL ratios were 3.1, 3.2, and 3.0,  
578 respectively, for AVANDIA 4 mg twice daily. The corresponding values for glyburide were 3.2,  
579 3.1, and 2.9. The differences in change from baseline between AVANDIA and glyburide at  
580 week 52 were statistically significant.

581 The pattern of LDL and HDL changes following therapy with AVANDIA in combination  
582 with other hypoglycemic agents were generally similar to those seen with AVANDIA in  
583 monotherapy.

584 The changes in triglycerides during therapy with AVANDIA were variable and were  
585 generally not statistically different from placebo or glyburide controls.

586

587 Table 9. Summary of Mean Lipid Changes in 26-Week Placebo-Controlled and 52-Week  
588 Glyburide-Controlled Monotherapy Trials

	Placebo-Controlled Trials			Glyburide-Controlled Trial			
	Week 26			Week 26 and Week 52			
	Placebo	AVANDIA		Glyburide Titration		AVANDIA 8 mg	
		4 mg daily <sup>a</sup>	8 mg daily <sup>a</sup>	Wk 26	Wk 52	Wk 26	Wk 52
<b>Free fatty acids</b>							
N	207	428	436	181	168	166	145
Baseline (mean)	18.1	17.5	17.9	26.4	26.4	26.9	26.6
% Change from baseline (mean)	+0.2%	-7.8%	-14.7%	-2.4%	-4.7%	-20.8%	-21.5%
<b>LDL</b>							
N	190	400	374	175	160	161	133
Baseline (mean)	123.7	126.8	125.3	142.7	141.9	142.1	142.1
% Change from baseline (mean)	+4.8%	+14.1%	+18.6%	-0.9%	-0.5%	+11.9%	+12.1%
<b>HDL</b>							
N	208	429	436	184	170	170	145
Baseline (mean)	44.1	44.4	43.0	47.2	47.7	48.4	48.3
% Change from baseline (mean)	+8.0%	+11.4%	+14.2%	+4.3%	+8.7%	+14.0%	+18.5%

589 <sup>a</sup> Once daily and twice daily dosing groups were combined.

590

591 **12.3 Pharmacokinetics**

592 Maximum plasma concentration ( $C_{max}$ ) and the area under the curve (AUC) of  
593 rosiglitazone increase in a dose-proportional manner over the therapeutic dose range (Table 10).  
594 The elimination half-life is 3 to 4 hours and is independent of dose.  
595

596 Table 10. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral  
597 Doses (N = 32)

Parameter	1 mg Fasting	2 mg Fasting	8 mg Fasting	8 mg Fed
AUC <sub>0-inf</sub> [ng•hr/mL]	358 (112)	733 (184)	2,971 (730)	2,890 (795)
C <sub>max</sub> [ng/mL]	76 (13)	156 (42)	598 (117)	432 (92)
Half-life [hr]	3.16 (0.72)	3.15 (0.39)	3.37 (0.63)	3.59 (0.70)
CL/F <sup>a</sup> [L/hr]	3.03 (0.87)	2.89 (0.71)	2.85 (0.69)	2.97 (0.81)

598 <sup>a</sup> CL/F = Oral clearance.

599

600 **Absorption:** The absolute bioavailability of rosiglitazone is 99%. Peak plasma  
601 concentrations are observed about 1 hour after dosing. Administration of rosiglitazone with food  
602 resulted in no change in overall exposure (AUC), but there was an approximately 28% decrease  
603 in  $C_{max}$  and a delay in  $T_{max}$  (1.75 hours). These changes are not likely to be clinically significant;  
604 therefore, AVANDIA may be administered with or without food.

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

608 **Metabolism:** Rosiglitazone is extensively metabolized with no unchanged drug excreted  
609 in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed  
610 by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably  
611 less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing  
612 activity of rosiglitazone.

613 In vitro data demonstrate that rosiglitazone is predominantly metabolized by Cytochrome  
614 P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway.

615 **Excretion:** Following oral or intravenous administration of [<sup>14</sup>C]rosiglitazone maleate,  
616 approximately 64% and 23% of the dose was eliminated in the urine and in the feces,  
617 respectively. The plasma half-life of [<sup>14</sup>C]related material ranged from 103 to 158 hours.

618 **Population Pharmacokinetics in Patients With Type 2 Diabetes:** Population  
619 pharmacokinetic analyses from 3 large clinical trials including 642 men and 405 women with  
620 type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not

621 influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral  
622 steady-state volume of distribution (V<sub>ss</sub>/F) were shown to increase with increases in body  
623 weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted  
624 CL/F and V<sub>ss</sub>/F values varied by <1.7-fold and <2.3-fold, respectively. Additionally,  
625 rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about  
626 15%) in female patients.

627 **Special Populations: Geriatric:** Results of the population pharmacokinetic analysis  
628 (n = 716 <65 years; n = 331 ≥65 years) showed that age does not significantly affect the  
629 pharmacokinetics of rosiglitazone.

630 **Gender:** Results of the population pharmacokinetics analysis showed that the mean oral  
631 clearance of rosiglitazone in female patients (n = 405) was approximately 6% lower compared to  
632 male patients of the same body weight (n = 642).

633 As monotherapy and in combination with metformin, AVANDIA improved glycemic  
634 control in both males and females. In metformin combination trials, efficacy was demonstrated  
635 with no gender differences in glycemic response.

636 In monotherapy trials, a greater therapeutic response was observed in females; however,  
637 in more obese patients, gender differences were less evident. For a given body mass index  
638 (BMI), females tend to have a greater fat mass than males. Since the molecular target PPAR<sub>γ</sub> is  
639 expressed in adipose tissues, this differentiating characteristic may account, at least in part, for  
640 the greater response to AVANDIA in females. Since therapy should be individualized, no dose  
641 adjustments are necessary based on gender alone.

642 **Hepatic Impairment:** Unbound oral clearance of rosiglitazone was significantly lower in  
643 patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy  
644 subjects. As a result, unbound C<sub>max</sub> and AUC<sub>0-inf</sub> were increased 2- and 3-fold, respectively.  
645 Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease,  
646 compared to healthy subjects.

647 Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence  
648 of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of  
649 normal) at baseline [see *Warnings and Precautions* (5.6)].

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

656 **Renal Impairment:** There are no clinically relevant differences in the pharmacokinetics  
657 of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent  
658 patients compared to subjects with normal renal function. No dosage adjustment is therefore  
659 required in such patients receiving AVANDIA. Since metformin is contraindicated in patients  
660 with renal impairment, coadministration of metformin with AVANDIA is contraindicated in

661 these patients.

662 *Race*: Results of a population pharmacokinetic analysis including subjects of Caucasian,  
663 black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of  
664 rosiglitazone.

## 665 **12.4 Drug-Drug Interactions**

666 Drugs That Inhibit, Induce, or are Metabolized by Cytochrome P450: In vitro drug  
667 metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at  
668 clinically relevant concentrations. In vitro data demonstrate that rosiglitazone is predominantly  
669 metabolized by CYP2C8, and to a lesser extent, 2C9. AVANDIA (4 mg twice daily) was shown  
670 to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral  
671 contraceptives (ethinyl estradiol and norethindrone), which are predominantly metabolized by  
672 CYP3A4.

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

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

681 Glyburide: AVANDIA (2 mg twice daily) taken concomitantly with glyburide (3.75 to  
682 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations  
683 in diabetic patients stabilized on glyburide therapy. Repeat doses of AVANDIA (8 mg once  
684 daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and  
685 C<sub>max</sub> of approximately 30%. In Japanese subjects, glyburide AUC and C<sub>max</sub> slightly increased  
686 following coadministration of AVANDIA.

687 Glimepiride: Single oral doses of glimepiride in 14 healthy adult subjects had no  
688 clinically significant effect on the steady-state pharmacokinetics of AVANDIA. No clinically  
689 significant reductions in glimepiride AUC and C<sub>max</sub> were observed after repeat doses of  
690 AVANDIA (8 mg once daily) for 8 days in healthy adult subjects.

691 Metformin: Concurrent administration of AVANDIA (2 mg twice daily) and metformin  
692 (500 mg twice daily) in healthy volunteers for 4 days had no effect on the steady-state  
693 pharmacokinetics of either metformin or rosiglitazone.

694 Acarbose: Coadministration of acarbose (100 mg three times daily) for 7 days in healthy  
695 volunteers had no clinically relevant effect on the pharmacokinetics of a single oral dose of  
696 AVANDIA.

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

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

701 Ethanol: A single administration of a moderate amount of alcohol did not increase the  
702 risk of acute hypoglycemia in type 2 diabetes mellitus patients treated with AVANDIA.

703 Ranitidine: Pretreatment with ranitidine (150 mg twice daily for 4 days) did not alter the  
704 pharmacokinetics of either single oral or intravenous doses of rosiglitazone in healthy volunteers.  
705 These results suggest that the absorption of oral rosiglitazone is not altered in conditions  
706 accompanied by increases in gastrointestinal pH.

## 707 **13 NONCLINICAL TOXICOLOGY**

### 708 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

709 Carcinogenesis: A 2-year carcinogenicity study was conducted in Charles River CD-1  
710 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately  
711 12 times human AUC at the maximum recommended human daily dose). Sprague-Dawley rats  
712 were dosed for 2 years by oral gavage at doses of 0.05, 0.3, and 2 mg/kg/day (highest dose  
713 equivalent to approximately 10 and 20 times human AUC at the maximum recommended human  
714 daily dose for male and female rats, respectively).

715 Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of  
716 adipose hyperplasia in the mouse at doses  $\geq 1.5$  mg/kg/day (approximately 2 times human AUC  
717 at the maximum recommended human daily dose). In rats, there was a significant increase in the  
718 incidence of benign adipose tissue tumors (lipomas) at doses  $\geq 0.3$  mg/kg/day (approximately  
719 2 times human AUC at the maximum recommended human daily dose). These proliferative  
720 changes in both species are considered due to the persistent pharmacological overstimulation of  
721 adipose tissue.

722 Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial  
723 assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in  
724 vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about  
725 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic  
726 activation.

727 Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats  
728 given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended  
729 human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility  
730 (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and  
731 estradiol (approximately 20 and 200 times human AUC at the maximum recommended human  
732 daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times  
733 human AUC at the maximum recommended human daily dose). In juvenile rats dosed from  
734 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male  
735 reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in  
736 females (approximately 68 times human AUC at the maximum recommended human daily  
737 dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human  
738 AUC at the maximum recommended human daily dose, respectively) diminished the follicular  
739 phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge,

740 lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears  
741 to be direct inhibition of ovarian steroidogenesis.

### 742 **13.2 Animal Toxicology**

743 Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs  
744 (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at  
745 the maximum recommended human daily dose, respectively). Effects in juvenile rats were  
746 consistent with those seen in adults. Morphometric measurement indicated that there was  
747 hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result  
748 of plasma volume expansion.

## 749 **14 CLINICAL STUDIES**

### 750 **14.1 Monotherapy**

751 In clinical trials, treatment with AVANDIA resulted in an improvement in glycemic  
752 control, as measured by FPG and HbA1c, with a concurrent reduction in insulin and C-peptide.  
753 Postprandial glucose and insulin were also reduced. This is consistent with the mechanism of  
754 action of AVANDIA as an insulin sensitizer.

755 The maximum recommended daily dose is 8 mg. Dose-ranging trials suggested that no  
756 additional benefit was obtained with a total daily dose of 12 mg.

757 Short-Term Clinical Trials: A total of 2,315 patients with type 2 diabetes, previously  
758 treated with diet alone or antidiabetic medication(s), were treated with AVANDIA as  
759 monotherapy in 6 double-blind trials, which included two 26-week placebo-controlled trials, one  
760 52-week glyburide-controlled trial, and 3 placebo-controlled dose-ranging trials of 8 to 12 weeks  
761 duration. Previous antidiabetic medication(s) were withdrawn and patients entered a 2 to 4 week  
762 placebo run-in period prior to randomization.

763 Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes  
764 (n = 1,401) with inadequate glycemic control (mean baseline FPG approximately 228 mg/dL  
765 [101 to 425 mg/dL] and mean baseline HbA1c 8.9% [5.2% to 16.2%]), were conducted.  
766 Treatment with AVANDIA produced statistically significant improvements in FPG and HbA1c  
767 compared to baseline and relative to placebo. Data from one of these trials are summarized in  
768 Table 11.

769

770 Table 11. Glycemic Parameters in a 26-Week Placebo-Controlled Trial

	Placebo	AVANDIA		AVANDIA	
		4 mg once daily	2 mg twice daily	8 mg once daily	4 mg twice daily
	N = 173	N = 180	N = 186	N = 181	N = 187
<b>FPG (mg/dL)</b>					
Baseline (mean)	225	229	225	228	228
Change from baseline (mean)	8	-25	-35	-42	-55
Difference from placebo (adjusted mean)	–	-31 <sup>a</sup>	-43 <sup>a</sup>	-49 <sup>a</sup>	-62 <sup>a</sup>
% of patients with ≥30 mg/dL decrease from baseline	19%	45%	54%	58%	70%
<b>HbA1c (%)</b>					
Baseline (mean)	8.9	8.9	8.9	8.9	9.0
Change from baseline (mean)	0.8	0.0	-0.1	-0.3	-0.7
Difference from placebo (adjusted mean)	–	-0.8 <sup>a</sup>	-0.9 <sup>a</sup>	-1.1 <sup>a</sup>	-1.5 <sup>a</sup>
% of patients with ≥0.7% decrease from baseline	9%	28%	29%	39%	54%

771 <sup>a</sup> *P* <0.0001 compared to placebo.

772

773 When administered at the same total daily dose, AVANDIA was generally more effective  
774 in reducing FPG and HbA1c when administered in divided doses twice daily compared to once  
775 daily doses. However, for HbA1c, the difference between the 4 mg once daily and 2 mg twice  
776 daily doses was not statistically significant.

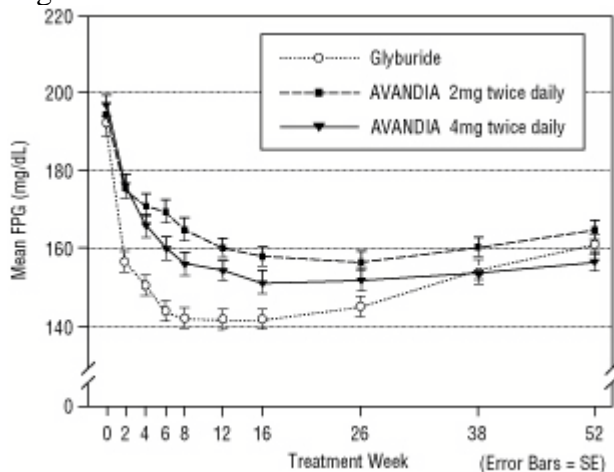
777 Long-Term Clinical Trials: Long-term maintenance of effect was evaluated in a  
778 52-week, double-blind, glyburide-controlled trial in patients with type 2 diabetes. Patients were  
779 randomized to treatment with AVANDIA 2 mg twice daily (N = 195) or AVANDIA 4 mg twice  
780 daily (N = 189) or glyburide (N = 202) for 52 weeks. Patients receiving glyburide were given an  
781 initial dosage of either 2.5 mg/day or 5.0 mg/day. The dosage was then titrated in 2.5 mg/day  
782 increments over the next 12 weeks, to a maximum dosage of 15.0 mg/day in order to optimize  
783 glycemic control. Thereafter, the glyburide dose was kept constant.

784 The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a  
785 statistically significant improvement in glycemic control from baseline (Figure 3 and Figure 4).  
786 At the end of week 52, the reduction from baseline in FPG and HbA1c was -40.8 mg/dL and  
787 -0.53% with AVANDIA 4 mg twice daily; -25.4 mg/dL and -0.27% with AVANDIA 2 mg twice  
788 daily; and -30.0 mg/dL and -0.72% with glyburide. For HbA1c, the difference between  
789 AVANDIA 4 mg twice daily and glyburide was not statistically significant at week 52. The  
790 initial fall in FPG with glyburide was greater than with AVANDIA; however, this effect was less  
791 durable over time. The improvement in glycemic control seen with AVANDIA 4 mg twice daily

792 at week 26 was maintained through week 52 of the trial.

793

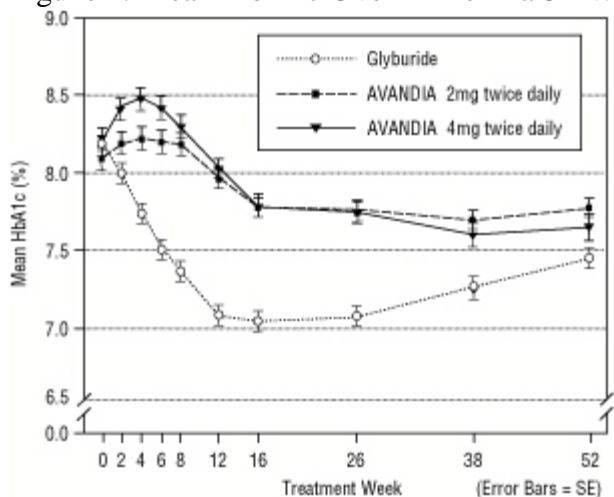
794 Figure 3. Mean FPG Over Time in a 52-Week Glyburide-Controlled Trial



795

796

797 Figure 4. Mean HbA1c Over Time in a 52-Week Glyburide-Controlled Trial



798

799

800 Hypoglycemia was reported in 12.1% of glyburide-treated patients versus 0.5% (2 mg  
801 twice daily) and 1.6% (4 mg twice daily) of patients treated with AVANDIA. The improvements  
802 in glycemic control were associated with a mean weight gain of 1.75 kg and 2.95 kg for patients  
803 treated with 2 mg and 4 mg twice daily of AVANDIA, respectively, versus 1.9 kg in  
804 glyburide-treated patients. In patients treated with AVANDIA, C-peptide, insulin, pro-insulin,  
805 and pro-insulin split products were significantly reduced in a dose-ordered fashion, compared to  
806 an increase in the glyburide-treated patients.

807

808 A Diabetes Outcome Progression Trial (ADOPT) was a multicenter, double-blind,  
809 controlled trial (N = 4,351) conducted over 4 to 6 years to compare the safety and efficacy of  
810 AVANDIA, metformin, and glyburide monotherapy in patients recently diagnosed with type 2  
diabetes mellitus ( $\leq 3$  years) inadequately controlled with diet and exercise. The mean age of

811 patients in this trial was 57 years and the majority of patients (83%) had no known history of  
812 cardiovascular disease. The mean baseline FPG and HbA1c were 152 mg/dL and 7.4%,  
813 respectively. Patients were randomized to receive either AVANDIA 4 mg once daily, glyburide  
814 2.5 mg once daily, or metformin 500 mg once daily, and doses were titrated to optimal glycemic  
815 control up to a maximum of 4 mg twice daily for AVANDIA, 7.5 mg twice daily for glyburide,  
816 and 1,000 mg twice daily for metformin. The primary efficacy outcome was time to consecutive  
817 FPG >180 mg/dL after at least 6 weeks of treatment at the maximum tolerated dose of study  
818 medication or time to inadequate glycemic control, as determined by an independent  
819 adjudication committee.

820 The cumulative incidence of the primary efficacy outcome at 5 years was 15% with  
821 AVANDIA, 21% with metformin, and 34% with glyburide (HR 0.68 [95% CI 0.55, 0.85] versus  
822 metformin, HR 0.37 [95% CI 0.30, 0.45] versus glyburide).

823 Cardiovascular and adverse event data (including effects on body weight and bone  
824 fracture) from ADOPT for AVANDIA, metformin, and glyburide are described in *Warnings and*  
825 *Precautions* (5.2, 5.5, and 5.8) and *Adverse Reactions* (6.1), respectively. As with all  
826 medications, efficacy results must be considered together with safety information to assess the  
827 potential benefit and risk for an individual patient.

#### 828 **14.2 Combination With Metformin or Sulfonylurea**

829 The addition of AVANDIA to either metformin or sulfonylurea resulted in significant  
830 reductions in hyperglycemia compared to either of these agents alone. These results are  
831 consistent with an additive effect on glycemic control when AVANDIA is used as combination  
832 therapy.

833 Combination With Metformin: A total of 670 patients with type 2 diabetes participated  
834 in two 26-week, randomized, double-blind, placebo/active-controlled trials designed to assess the  
835 efficacy of AVANDIA in combination with metformin. AVANDIA, administered in either once  
836 daily or twice daily dosing regimens, was added to the therapy of patients who were inadequately  
837 controlled on a maximum dose (2.5 grams/day) of metformin.

838 In one trial, patients inadequately controlled on 2.5 grams/day of metformin (mean  
839 baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were randomized to receive 4 mg of  
840 AVANDIA once daily, 8 mg of AVANDIA once daily, or placebo in addition to metformin. A  
841 statistically significant improvement in FPG and HbA1c was observed in patients treated with  
842 the combinations of metformin and 4 mg of AVANDIA once daily and 8 mg of AVANDIA once  
843 daily, versus patients continued on metformin alone (Table 12).

844

845 Table 12. Glycemic Parameters in a 26-Week Combination Trial of AVANDIA Plus  
846 Metformin

	<b>Metformin</b>	<b>AVANDIA 4 mg once daily + metformin</b>	<b>AVANDIA 8 mg once daily + metformin</b>
	N = 113	N = 116	N = 110
<b>FPG (mg/dL)</b>			
Baseline (mean)	214	215	220
Change from baseline (mean)	6	-33	-48
Difference from metformin alone (adjusted mean)	–	-40 <sup>a</sup>	-53 <sup>a</sup>
% of patients with ≥30 mg/dL decrease from baseline	20%	45%	61%
<b>HbA1c (%)</b>			
Baseline (mean)	8.6	8.9	8.9
Change from baseline (mean)	0.5	-0.6	-0.8
Difference from metformin alone (adjusted mean)	–	-1.0 <sup>a</sup>	-1.2 <sup>a</sup>
% of patients with ≥0.7% decrease from baseline	11%	45%	52%

847 <sup>a</sup> *P* <0.0001 compared to metformin.

848

849 In a second 26-week trial, patients with type 2 diabetes inadequately controlled on  
850 2.5 grams/day of metformin who were randomized to receive the combination of AVANDIA  
851 4 mg twice daily and metformin (N = 105) showed a statistically significant improvement in  
852 glycemic control with a mean treatment effect for FPG of -56 mg/dL and a mean treatment effect  
853 for HbA1c of -0.8% over metformin alone. The combination of metformin and AVANDIA  
854 resulted in lower levels of FPG and HbA1c than either agent alone.

855 Patients who were inadequately controlled on a maximum dose (2.5 grams/day) of  
856 metformin and who were switched to monotherapy with AVANDIA demonstrated loss of  
857 glycemic control, as evidenced by increases in FPG and HbA1c. In this group, increases in LDL  
858 and VLDL were also seen.

859 **Combination With a Sulfonylurea:** A total of 3,457 patients with type 2 diabetes  
860 participated in ten 24- to 26-week randomized, double-blind, placebo/active-controlled trials and  
861 one 2-year double-blind, active-controlled trial in elderly patients designed to assess the efficacy  
862 and safety of AVANDIA in combination with a sulfonylurea. AVANDIA 2 mg, 4 mg, or 8 mg  
863 daily was administered, either once daily (3 trials) or in divided doses twice daily (7 trials), to  
864 patients inadequately controlled on a submaximal or maximal dose of sulfonylurea.

865 In these trials, the combination of AVANDIA 4 mg or 8 mg daily (administered as single  
866 or twice daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c compared

867 to placebo plus sulfonylurea or further up-titration of the sulfonylurea. Table 13 shows pooled  
868 data for 8 trials in which AVANDIA added to sulfonylurea was compared to placebo plus  
869 sulfonylurea.  
870

871 Table 13. Glycemic Parameters in 24- to 26-Week Combination Trials of AVANDIA Plus  
872 Sulfonylurea

Twice Daily Divided Dosing (5 Trials)	Sulfonylurea	AVANDIA 2 mg twice daily + sulfonylurea	Sulfonylurea	AVANDIA 4 mg twice daily + sulfonylurea
	N = 397	N = 497	N = 248	N = 346
<b>FPG (mg/dL)</b>				
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%
<b>HbA1c (%)</b>				
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%
Once Daily Dosing (3 Trials)	Sulfonylurea	AVANDIA 4 mg once daily + sulfonylurea	Sulfonylurea	AVANDIA 8 mg once daily + sulfonylurea
	N = 172	N = 172	N = 173	N = 176
<b>FPG (mg/dL)</b>				
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%
<b>HbA1c (%)</b>				
Baseline (mean)	8.6	8.8	8.9	8.9
Change from baseline (mean)	0.4	-0.5	0.1	-1.2
Difference from sulfonylurea alone (adjusted mean)	–	-0.9 <sup>a</sup>	–	-1.4 <sup>a</sup>
% of patients with ≥0.7% decrease from baseline	11%	36%	20%	68%

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

874

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

878 In a 2-year double-blind trial, elderly patients (aged 59 to 89 years) on half-maximal  
879 sulfonylurea (glipizide 10 mg twice daily) were randomized to the addition of AVANDIA  
880 (n = 115, 4 mg once daily to 8 mg as needed) or to continued up-titration of glipizide (n = 110),  
881 to a maximum of 20 mg twice daily. Mean baseline FPG and HbA1c were 157 mg/dL and  
882 7.72%, respectively, for the AVANDIA plus glipizide arm and 159 mg/dL and 7.65%,  
883 respectively, for the glipizide up-titration arm. Loss of glycemic control (FPG  $\geq$ 180 mg/dL)  
884 occurred in a significantly lower proportion of patients (2%) on AVANDIA plus glipizide  
885 compared to patients in the glipizide up-titration arm (28.7%). About 78% of the patients on  
886 combination therapy completed the 2 years of therapy while only 51% completed on glipizide  
887 monotherapy. The effect of combination therapy on FPG and HbA1c was durable over the 2-year  
888 trial period, with patients achieving a mean of 132 mg/dL for FPG and a mean of 6.98% for  
889 HbA1c compared to no change on the glipizide arm.

### 890 **14.3 Combination With Sulfonylurea Plus Metformin**

891 In two 24- to 26-week, double-blind, placebo-controlled, trials designed to assess the  
892 efficacy and safety of AVANDIA in combination with sulfonylurea plus metformin, AVANDIA  
893 4 mg or 8 mg daily, was administered in divided doses twice daily, to patients inadequately  
894 controlled on submaximal (10 mg) and maximal (20 mg) doses of glyburide and maximal dose  
895 of metformin (2 g/day). A statistically significant improvement in FPG and HbA1c was observed  
896 in patients treated with the combinations of sulfonylurea plus metformin and 4 mg of AVANDIA  
897 and 8 mg of AVANDIA versus patients continued on sulfonylurea plus metformin, as shown in  
898 Table 14.

899

900 Table 14. Glycemic Parameters in a 26-Week Combination Trial of AVANDIA Plus  
901 Sulfonylurea and Metformin

	<b>Sulfonylurea + metformin</b>	<b>AVANDIA 2 mg twice daily + sulfonylurea + metformin</b>	<b>AVANDIA 4 mg twice daily + sulfonylurea + metformin</b>
	N = 273	N = 276	N = 277
<b>FPG (mg/dL)</b>			
Baseline (mean)	189	190	192
Change from baseline (mean)	14	-19	-40
Difference from sulfonylurea plus metformin (adjusted mean)	–	-30 <sup>a</sup>	-52 <sup>a</sup>
% of patients with ≥30 mg/dL decrease from baseline	16%	46%	62%
<b>HbA1c (%)</b>			
Baseline (mean)	8.7	8.6	8.7
Change from baseline (mean)	0.2	-0.4	-0.9
Difference from sulfonylurea plus metformin (adjusted mean)	–	-0.6 <sup>a</sup>	-1.1 <sup>a</sup>
% of patients with ≥0.7% decrease from baseline	16%	39%	63%

902 <sup>a</sup> P <0.0001 compared to placebo.  
903

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## 935 **16 HOW SUPPLIED/STORAGE AND HANDLING**

936 Each pentagonal film-coated TILTAB tablet contains rosiglitazone as the maleate as  
937 follows: 2 mg–pink, debossed with SB on one side and 2 on the other; 4 mg–orange, debossed  
938 with SB on one side and 4 on the other; 8 mg–red-brown, debossed with SB on one side and 8 on  
939 the other.

940 2 mg bottles of 60: NDC 0173-0834-18

941 4 mg bottles of 30: NDC 0173-0835-13

942 8 mg bottles of 30: NDC 0173-0836-13

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

## 945 **17 PATIENT COUNSELING INFORMATION**

946 See Medication Guide.

### 947 **17.1 Patient Advice**

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

951 Patients should be informed of the risks and benefits of AVANDIA. AVANDIA should  
952 only be taken by adults with type 2 diabetes who are already taking AVANDIA, or who are not  
953 already taking AVANDIA and are unable to achieve adequate glycemic control on other diabetes  
954 medications, and, in consultation with their healthcare provider, have decided not to take  
955 pioglitazone (ACTOS) for medical reasons. Inform patients that they must be enrolled in the  
956 AVANDIA-Rosiglitazone Medicines Access Program in order to receive AVANDIA.

957 Patients should be informed of the following:

- 958 • AVANDIA is not recommended for patients with symptomatic heart failure.
- 959 • Results of a set of clinical trials suggest that treatment with AVANDIA is associated with an  
960 increased risk for myocardial infarction (heart attack), especially in patients taking insulin.  
961 Clinical trials have not shown any difference between AVANDIA and comparator  
962 medications in overall mortality or CV-related mortality.
- 963 • AVANDIA is not recommended for patients who are taking insulin.
- 964 • Management of type 2 diabetes should include diet control. Caloric restriction, weight loss,  
965 and exercise are essential for the proper treatment of the diabetic patient because they help  
966 improve insulin sensitivity. This is important not only in the primary treatment of type 2  
967 diabetes, but in maintaining the efficacy of drug therapy.
- 968 • It is important to adhere to dietary instructions and to regularly have blood glucose and  
969 glycosylated hemoglobin tested. It can take 2 weeks to see a reduction in blood glucose and 2  
970 to 3 months to see the full effect of AVANDIA.
- 971 • Blood will be drawn to check their liver function prior to the start of therapy and periodically  
972 thereafter per the clinical judgment of the healthcare professional. Patients with unexplained  
973 symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should  
974 immediately report these symptoms to their physician.
- 975 • Patients who experience an unusually rapid increase in weight or edema or who develop  
976 shortness of breath or other symptoms of heart failure while on AVANDIA should  
977 immediately report these symptoms to their physician.
- 978 • AVANDIA can be taken with or without meals.
- 979 • When using AVANDIA in combination with other hypoglycemic agents, the risk of  
980 hypoglycemia, its symptoms and treatment, and conditions that predispose to its development  
981 should be explained to patients and their family members.
- 982 • Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some  
983 premenopausal anovulatory women. As a result, these patients may be at an increased risk for  
984 pregnancy while taking AVANDIA. Thus, adequate contraception in premenopausal women  
985 should be recommended. This possible effect has not been specifically investigated in  
986 clinical trials so the frequency of this occurrence is not known.

987

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993 Research Triangle Park, NC 27709

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