

## 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

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)

### RECENT MAJOR CHANGES

Boxed Warning, AVANDIA-Rosiglitazone Medicines Access Program removal	05/2014
Indications and Usage, patient population restrictions removal (1)	05/2014
Contraindications (4)	05/2014
Warnings and Precautions, Cardiac Failure (5.1)	05/2014
Warnings and Precautions, Major Adverse Cardiovascular Events (5.2)	05/2014
Warnings and Precautions, Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program removal (formerly 5.3)	05/2014

### INDICATIONS AND USAGE

AVANDIA is a thiazolidinedione antidiabetic agent indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

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

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

### WARNINGS and PRECAUTIONS

- 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)
- Meta-analysis of 52 mostly short-term trials suggested a potential risk of ischemic cardiovascular (CV) events relative to placebo, not confirmed in a long-term CV outcome trial versus metformin or sulfonylurea. (5.2)
- Dose-related edema (5.3), weight gain (5.4), and anemia (5.8) may occur.
- Macular edema has been reported. (5.6)
- Increased incidence of bone fracture. (5.7)

### 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)

### USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2014

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**This label may not be the latest approved by FDA.  
For current labeling information, please visit <https://www.fda.gov/drugsatfda>**

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

## 1 FULL PRESCRIBING INFORMATION

### 2 **WARNING: CONGESTIVE HEART FAILURE**

- 3 ● **Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure**  
4 **in some patients [see Warnings and Precautions (5.1)]. After initiation of AVANDIA, and**  
5 **after dose increases, observe patients carefully for signs and symptoms of heart failure**  
6 **(including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and**  
7 **symptoms develop, the heart failure should be managed according to current standards**  
8 **of care. Furthermore, discontinuation or dose reduction of AVANDIA must be**  
9 **considered.**
- 10 ● **AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of**  
11 **AVANDIA in patients with established NYHA Class III or IV heart failure is**  
12 **contraindicated. [See Contraindications (4), Warnings and Precautions (5.1).]**

### 13 **1 INDICATIONS AND USAGE**

14 AVANDIA<sup>®</sup> is a thiazolidinedione antidiabetic agent indicated as an adjunct to diet and  
15 exercise to improve glycemic control in adults with type 2 diabetes mellitus.

#### 16 **Important Limitations of Use:**

- 17 ● Due to its mechanism of action, AVANDIA is active only in the presence of endogenous  
18 insulin. Therefore, AVANDIA should not be used in patients with type 1 diabetes mellitus or  
19 for the treatment of diabetic ketoacidosis.
- 20 ● The coadministration of AVANDIA and insulin is not recommended [see Warnings and  
21 *Precautions (5.1)*].

### 22 **2 DOSAGE AND ADMINISTRATION**

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

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

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

#### 32 **2.1 Specific Patient Populations**

33 **Renal Impairment:** No dosage adjustment is necessary when AVANDIA is used as  
34 monotherapy in patients with renal impairment. Since metformin is contraindicated in such  
35 patients, concomitant administration of metformin and AVANDIA is also contraindicated in

36 patients with renal impairment.

37 **Hepatic Impairment:** Liver enzymes should be measured prior to initiating treatment  
38 with AVANDIA. Therapy with AVANDIA should not be initiated if the patient exhibits clinical  
39 evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit  
40 of normal at start of therapy). After initiation of AVANDIA, liver enzymes should be monitored  
41 periodically per the clinical judgment of the healthcare professional. [See Warnings and  
42 Precautions (5.5), Clinical Pharmacology (12.3).]

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

### 45 **3 DOSAGE FORMS AND STRENGTHS**

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

- 47 • 2 mg – pink, debossed with GSK on one side and 2 on the other
- 48 • 4 mg – orange, debossed with GSK on one side and 4 on the other
- 49 • 8 mg – red-brown, debossed with GSK on one side and 8 on the other

### 50 **4 CONTRAINDICATIONS**

- 51 • Initiation of AVANDIA in patients with established New York Heart Association (NYHA)  
52 Class III or IV heart failure is contraindicated [see Boxed Warning].
- 53 • Use in patients with a history of a hypersensitivity reaction to rosiglitazone or any of the  
54 product's ingredients.

### 55 **5 WARNINGS AND PRECAUTIONS**

#### 56 **5.1 Cardiac Failure**

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

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

72

73 **Table 1. Emergent Cardiovascular Adverse Events in Patients With Congestive Heart**

74 **Failure (NYHA Class I and II) Treated With AVANDIA or Placebo (in Addition to**  
75 **Background Antidiabetic and CHF Therapy)**

Events	AVANDIA N = 110 n (%)	Placebo 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%)

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

77

78 In a long-term, cardiovascular outcome trial (RECORD) in patients with type 2 diabetes  
79 [see *Adverse Reactions (6.1)*], the incidence of heart failure was higher in patients treated with  
80 AVANDIA [2.7% (61/2,220) compared with active control 1.3% (29/2,227), HR 2.10 (95% CI:  
81 1.35, 3.27)].

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

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

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

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

96 In 7 controlled, randomized, double-blind trials which had durations from 16 to 26 weeks  
97 and which were included in a meta-analysis [see *Warnings and Precautions (5.2)*], patients with

98 type 2 diabetes mellitus were randomized to coadministration of AVANDIA and insulin  
99 (N = 1,018) or insulin (N = 815). In these 7 trials, AVANDIA was added to insulin. These trials  
100 included patients with long-standing diabetes (median duration of 12 years) and a high  
101 prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy,  
102 ischemic heart disease, vascular disease, and congestive heart failure. The total number of  
103 patients with emergent congestive heart failure was 23 (2.3%) and 8 (1.0%) in the group  
104 receiving AVANDIA plus insulin and the insulin group, respectively.

105 Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing  
106 AVANDIA to Pioglitazone: Three observational studies in elderly diabetic patients (age 65  
107 years and older) found that AVANDIA statistically significantly increased the risk of  
108 hospitalized heart failure compared to use of pioglitazone. One other observational study in  
109 patients with a mean age of 54 years, which also included an analysis in a subpopulation of  
110 patients >65 years of age, found no statistically significant increase in emergency department  
111 visits or hospitalization for heart failure in patients treated with AVANDIA compared to  
112 pioglitazone in the older subgroup.

## 113 **5.2 Major Adverse Cardiovascular Events**

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

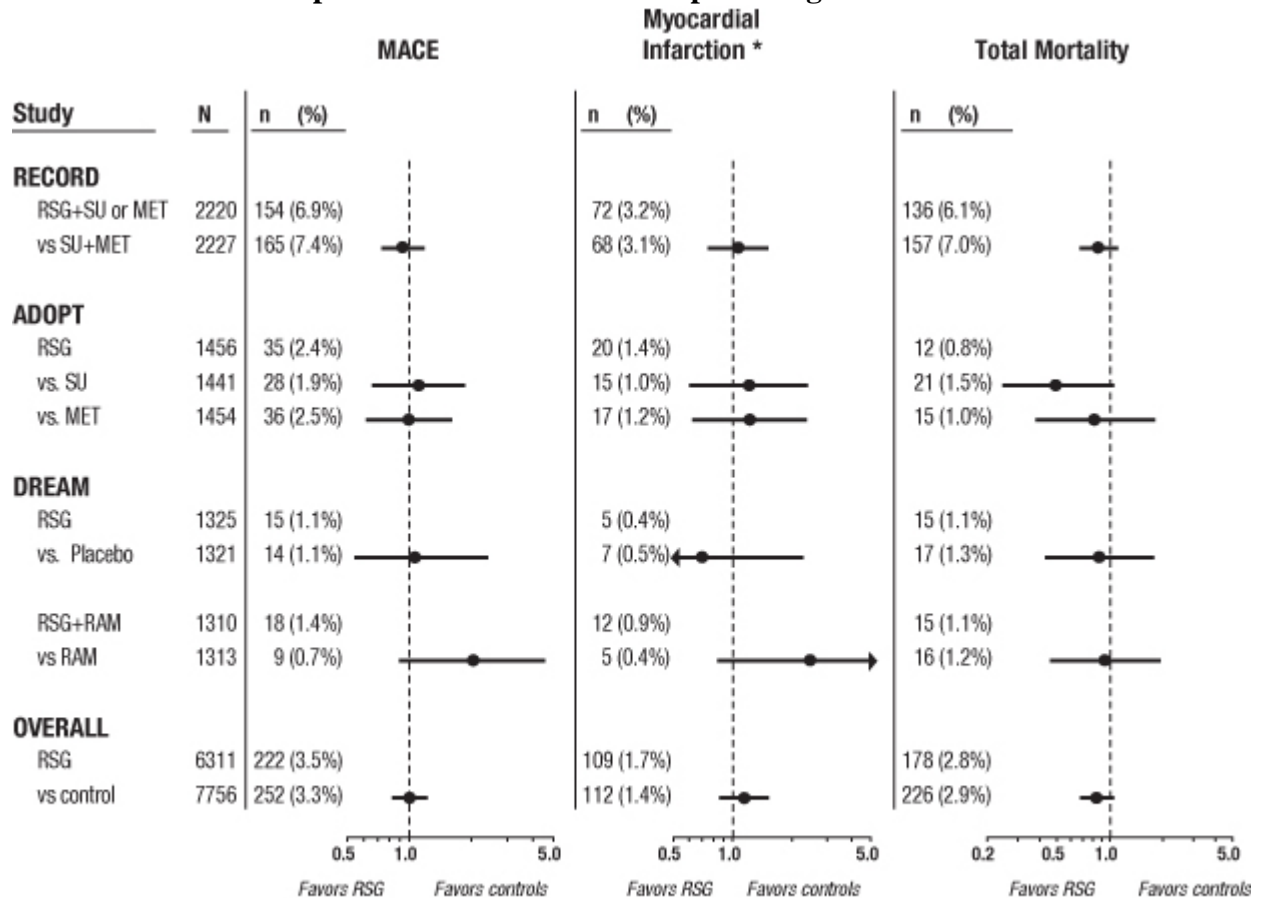
119 Cardiovascular Events in Large, Long-term, Prospective, Randomized,  
120 Controlled Trials of AVANDIA: RECORD, a prospectively designed cardiovascular outcome  
121 trial (mean follow-up 5.5 years; 4,447 patients), compared the addition of AVANDIA to  
122 metformin or a sulfonylurea (N = 2,220) with a control group of metformin plus sulfonylurea  
123 (N = 2,227) in patients with type 2 diabetes [see *Adverse Reactions (6.1)*]. Non-inferiority was  
124 demonstrated for the primary endpoint, cardiovascular hospitalization or cardiovascular death,  
125 for AVANDIA compared with control [HR 0.99 (95% CI: 0.85, 1.16)] demonstrating no overall  
126 increased risk in cardiovascular morbidity or mortality. The hazard ratios for total mortality and  
127 MACE were consistent with the primary endpoint and the 95% CI similarly excluded a 20%  
128 increase in risk for AVANDIA. The hazard ratios for the components of MACE were 0.72 (95%  
129 CI: 0.49, 1.06) for stroke, 1.14 (95% CI: 0.80, 1.63) for myocardial infarction, and 0.84 (95% CI:  
130 0.59, 1.18) for cardiovascular death.

131 The results of RECORD are consistent with the findings of 2 earlier long-term,  
132 prospective, randomized, controlled clinical trials (each trial >3 years' duration; total of 9,620  
133 patients) (see Figure 1). In patients with impaired glucose tolerance (DREAM trial), although the  
134 incidence of cardiovascular events was higher among subjects who were randomized to  
135 AVANDIA in combination with ramipril than among subjects randomized to ramipril alone, no  
136 statistically significant differences were observed for MACE and its components between  
137 AVANDIA and placebo. In type 2 diabetes patients who were initiating oral agent monotherapy

138 (ADOPT trial), no statistically significant differences were observed for MACE and its  
139 components between AVANDIA and metformin or a sulfonylurea.

140

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



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

143

144

145 **Cardiovascular Events in a Group of 52 Clinical Trials:** In a meta-analysis of 52  
146 double-blind, randomized, controlled clinical trials designed to assess glucose-lowering efficacy  
147 in type 2 diabetes (mean duration 6 months), a statistically significant increased risk of  
148 myocardial infarction with AVANDIA versus pooled comparators was observed [0.4% versus  
149 0.3%; OR 1.8, (95% CI: 1.03, 3.25)]. A statistically non-significant increased risk of MACE was  
150 observed with AVANDIA versus pooled comparators (OR 1.44, 95% CI: 0.95, 2.20). In the  
151 placebo-controlled trials, a statistically significant increased risk of myocardial infarction [0.4%  
152 versus 0.2%, OR 2.23 (95% CI: 1.14, 4.64)] and statistically non-significant increased risk of  
153 MACE [0.7% versus 0.5%, OR 1.53 (95% CI: 0.94, 2.54)] with AVANDIA **were was** observed.  
154 In the active-controlled trials, there was no increased risk of myocardial infarction or MACE.

155

**Mortality in Observational Studies of AVANDIA Compared to Pioglitazone:** Three

156 observational studies in elderly diabetic patients (age 65 years and older) found that AVANDIA  
157 statistically significantly increased the risk of all-cause mortality compared to use of  
158 pioglitazone. One observational study in patients with a mean age of 54 years found no  
159 difference in all-cause mortality between patients treated with AVANDIA compared to  
160 pioglitazone and reported similar results in the subpopulation of patients >65 years of age. One  
161 additional small, prospective, observational study found no statistically significant differences  
162 for CV mortality and all-cause mortality in patients treated with AVANDIA compared to  
163 pioglitazone.

### 164 **5.3 Edema**

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

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

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

### 176 **5.4 Weight Gain**

177 Dose-related weight gain was seen with AVANDIA alone and in combination with other  
178 hypoglycemic agents (Table 2). The mechanism of weight gain is unclear but probably involves  
179 a combination of fluid retention and fat accumulation.

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

184

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

Monotherapy	Duration	Control Group		AVANDIA 4 mg	AVANDIA 8 mg
			Median (25 <sup>th</sup> , 75 <sup>th</sup> percentiles)	Median (25 <sup>th</sup> , 75 <sup>th</sup> percentiles)	Median (25 <sup>th</sup> , 75 <sup>th</sup> percentiles)
	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

186

187 In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed  
188 with type 2 diabetes not previously treated with antidiabetic medication [see *Clinical Studies*  
189 (14.1)], the median weight change (25<sup>th</sup>, 75<sup>th</sup> percentiles) from baseline at 4 years was 3.5 kg  
190 (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.

191 In a 24-week trial in pediatric patients aged 10 to 17 years treated with AVANDIA 4 to  
192 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.

193 **5.5 Hepatic Effects**

194 Liver enzymes should be measured prior to the initiation of therapy with AVANDIA in  
195 all patients and periodically thereafter per the clinical judgment of the healthcare professional.  
196 Therapy with AVANDIA should not be initiated in patients with increased baseline liver enzyme  
197 levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes (ALT  
198 levels ≤2.5X upper limit of normal) at baseline or during therapy with AVANDIA should be  
199 evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of,  
200 therapy with AVANDIA in patients with mild liver enzyme elevations should proceed with  
201 caution and include close clinical follow-up, including liver enzyme monitoring, to determine if  
202 the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X the  
203 upper limit of normal in patients on therapy with AVANDIA, liver enzyme levels should be  
204 rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with  
205 AVANDIA should be discontinued.

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

## 211 **5.6 Macular Edema**

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

## 222 **5.7 Fractures**

223 Long-term trials (ADOPT and RECORD) show an increased incidence of bone fracture  
224 in patients, particularly female patients, taking AVANDIA [see *Adverse Reactions* (6.1)]. This  
225 increased incidence was noted after the first year of treatment and persisted during the course of  
226 the trial. The majority of the fractures in the women who received AVANDIA occurred in the  
227 upper arm, hand, and foot. These sites of fracture are different from those usually associated with  
228 postmenopausal osteoporosis (e.g., hip or spine). Other trials suggest that this risk may also  
229 apply to men, although the risk of fracture among women appears higher than that among men.  
230 The risk of fracture should be considered in the care of patients treated with AVANDIA, and  
231 attention given to assessing and maintaining bone health according to current standards of care.

## 232 **5.8 Hematologic Effects**

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

## 236 **5.9 Diabetes and Blood Glucose Control**

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

239 Periodic fasting blood glucose and HbA1c measurements should be performed to monitor  
240 therapeutic response.

## 241 **5.10 Ovulation**

242 Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some  
243 premenopausal anovulatory women. As a result, these patients may be at an increased risk for  
244 pregnancy while taking AVANDIA [see *Use in Specific Populations* (8.1)]. Thus, adequate  
245 contraception in premenopausal women should be recommended. This possible effect has not

246 been specifically investigated in clinical trials; therefore, the frequency of this occurrence is not  
247 known.

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

## 251 **6 ADVERSE REACTIONS**

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

- 253 • Cardiac Failure [*see Warnings and Precautions (5.1)*]
- 254 • Major Adverse Cardiovascular Events [*see Warnings and Precautions (5.2)*]
- 255 • Edema [*see Warnings and Precautions (5.3)*]
- 256 • Weight Gain [*see Warnings and Precautions (5.4)*]
- 257 • Hepatic Effects [*see Warnings and Precautions (5.5)*]
- 258 • Macular Edema [*see Warnings and Precautions (5.6)*]
- 259 • Fractures [*see Warnings and Precautions (5.7)*]
- 260 • Hematologic Effects [*see Warnings and Precautions (5.8)*]
- 261 • Ovulation [*see Warnings and Precautions (5.10)*]

### 262 **6.1 Clinical Trial Experience**

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

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

268 *Short-term Trials of AVANDIA as Monotherapy and in Combination With Other*  
269 *Hypoglycemic Agents:* The incidence and types of adverse events reported in short-term  
270 clinical trials of AVANDIA as monotherapy are shown in Table 3.

271

272 **Table 3. Adverse Events ( $\geq 5\%$  in any Treatment Group) Reported by Patients in Short-**  
273 **term<sup>a</sup> Double-blind Clinical Trials With AVANDIA as Monotherapy**

	<b>AVANDIA Monotherapy N = 2,526</b>	<b>Placebo N = 601</b>	<b>Metformin N = 225</b>	<b>Sulfonylureas<sup>b</sup> N = 626</b>
<b>Preferred Term</b>	<b>%</b>	<b>%</b>	<b>%</b>	<b>%</b>
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

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

275 <sup>b</sup> Includes patients receiving glyburide (N = 514), gliclazide (N = 91), or glipizide (N = 21).  
276

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

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

283 In double-blind trials, anemia was reported in 1.9% of patients receiving AVANDIA as  
284 monotherapy compared with 0.7% on placebo, 0.6% on sulfonylureas, and 2.2% on metformin.  
285 Reports of anemia were greater in patients treated with a combination of AVANDIA and  
286 metformin (7.1%) and with a combination of AVANDIA and a sulfonylurea plus metformin  
287 (6.7%) compared with monotherapy with AVANDIA or in combination with a sulfonylurea  
288 (2.3%). Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin  
289 combination clinical trials may have contributed to the higher reporting rate of anemia in these  
290 trials [see *Adverse Reactions (6.2)*].

291 In clinical trials, edema was reported in 4.8% of patients receiving AVANDIA as  
292 monotherapy compared with 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin.  
293 The reporting rate of edema was higher for AVANDIA 8 mg in sulfonylurea combinations  
294 (12.4%) compared with other combinations, with the exception of insulin. Edema was reported  
295 in 14.7% of patients receiving AVANDIA in the insulin combination trials compared with 5.4%  
296 on insulin alone. Reports of new onset or exacerbation of congestive heart failure occurred at  
297 rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with

298 AVANDIA [see Boxed Warning, Warnings and Precautions (5.1)].

299 In controlled combination therapy trials with sulfonylureas, mild to moderate  
300 hypoglycemic symptoms, which appear to be dose related, were reported. Few patients were  
301 withdrawn for hypoglycemia (<1%) and few episodes of hypoglycemia were considered to be  
302 severe (<1%). Hypoglycemia was the most frequently reported adverse event in the fixed-dose  
303 insulin combination trials, although few patients withdrew for hypoglycemia (4 of 408 for  
304 AVANDIA plus insulin and 1 of 203 for insulin alone). Rates of hypoglycemia, confirmed by  
305 capillary blood glucose concentration  $\leq$ 50 mg/dL, were 6% for insulin alone and 12% (4 mg) and  
306 14% (8 mg) for insulin in combination with AVANDIA. [See Warnings and Precautions (5.9).]

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

313 In ADOPT, fractures were reported in a greater number of women treated with  
314 AVANDIA (9.3%, 2.7/100 patient-years) compared with glyburide (3.5%, 1.3/100 patient-years)  
315 or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who  
316 received rosiglitazone were reported in the upper arm, hand, and foot. [See Warnings and  
317 Precautions (5.7).] The observed incidence of fractures for male patients was similar among the  
318 3 treatment groups.

319  
320 **Table 4. On-therapy Adverse Events [ $\geq$ 5 Events/100 Patient-Years (PY)] in any Treatment**  
321 **Group Reported in a 4- to 6-Year Clinical Trial of AVANDIA as Monotherapy (ADOPT)**

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

322  
323 **Long-term Trial of AVANDIA as Combination Therapy (RECORD):** RECORD  
324 (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) was a  
325 multicenter, randomized, open-label, non-inferiority trial in subjects with type 2 diabetes  
326 inadequately controlled on maximum doses of metformin or sulfonylurea (glyburide, gliclazide,  
327 or glimepiride) to compare the time to reach the combined cardiovascular endpoint of

328 cardiovascular death or cardiovascular hospitalization between patients randomized to the  
329 addition of AVANDIA versus metformin or sulfonylurea. The trial included patients who have  
330 failed metformin or sulfonylurea monotherapy; those who failed metformin (n = 2,222) were  
331 randomized to receive either AVANDIA as add-on therapy (n = 1,117) or add-on sulfonylurea  
332 (n = 1,105), and those who failed sulfonylurea (n = 2,225) were randomized to receive either  
333 AVANDIA as add-on therapy (n = 1,103) or add-on metformin (n = 1,122). Patients were treated  
334 to target HbA1c  $\leq$ 7% throughout the trial.

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

341  
342

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

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

343

344 There was an increased incidence of bone fracture for subjects randomized to AVANDIA  
345 in addition to metformin or sulfonylurea compared with those randomized to metformin plus  
346 sulfonylurea (8.3% versus 5.3%) [see *Warnings and Precautions (5.7)*]. The majority of  
347 fractures were reported in the upper limbs and distal lower limbs. The risk of fracture appeared  
348 to be higher in females relative to control (11.5% versus 6.3%), than in males relative to control  
349 (5.3% versus 4.3%). Additional data are necessary to determine whether there is an increased  
350 risk of fracture in males after a longer period of follow-up.

351 Pediatric: AVANDIA has been evaluated for safety in a single, active-controlled trial of  
352 pediatric patients with type 2 diabetes in which 99 were treated with AVANDIA and 101 were  
353 treated with metformin. The most common adverse reactions (>10%) without regard to causality  
354 for either AVANDIA or metformin were headache (17% versus 14%), nausea (4% versus 11%),  
355 nasopharyngitis (3% versus 12%), and diarrhea (1% versus 13%). In this trial, one case of  
356 diabetic ketoacidosis was reported in the metformin group. In addition, there were 3 patients in  
357 the rosiglitazone group who had FPG of approximately 300 mg/dL, 2+ ketonuria, and an

358 elevated anion gap.

## 359 **6.2 Laboratory Abnormalities**

360 Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a dose-related  
361 fashion in adult patients treated with AVANDIA (mean decreases in individual trials as much as  
362 1.0 g/dL hemoglobin and as much as 3.3% hematocrit). The changes occurred primarily during  
363 the first 3 months following initiation of therapy with AVANDIA or following a dose increase in  
364 AVANDIA. The time course and magnitude of decreases were similar in patients treated with a  
365 combination of AVANDIA and other hypoglycemic agents or monotherapy with AVANDIA.  
366 Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin  
367 combination trials and may have contributed to the higher reporting rate of anemia. In a single  
368 trial in pediatric patients, decreases in hemoglobin and hematocrit (mean decreases of 0.29 g/dL  
369 and 0.95%, respectively) were reported. Small decreases in hemoglobin and hematocrit have also  
370 been reported in pediatric patients treated with AVANDIA. White blood cell counts also  
371 decreased slightly in adult patients treated with AVANDIA. Decreases in hematologic  
372 parameters may be related to increased plasma volume observed with treatment with  
373 AVANDIA.

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

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

381 In pre-approval controlled trials, 0.2% of patients treated with AVANDIA had elevations  
382 in ALT >3X the upper limit of normal compared with 0.2% on placebo and 0.5% on active  
383 comparators. The ALT elevations in patients treated with AVANDIA were reversible.  
384 Hyperbilirubinemia was found in 0.3% of patients treated with AVANDIA compared with 0.9%  
385 treated with placebo and 1% in patients treated with active comparators. In pre-approval clinical  
386 trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. [*See*  
387 *Warnings and Precautions (5.5).*]

388 In the 4- to 6-year ADOPT trial, patients treated with AVANDIA (4,954 patient-years  
389 exposure), glyburide (4,244 patient-years exposure), or metformin (4,906 patient-years  
390 exposure), as monotherapy, had the same rate of ALT increase to >3X upper limit of normal  
391 (0.3 per 100 patient-years exposure).

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

## 396 **6.3 Postmarketing Experience**

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

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

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

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

408 There are postmarketing reports with AVANDIA of rash, pruritus, urticaria, angioedema,  
409 anaphylactic reaction, Stevens-Johnson syndrome [*see Contraindications (4)*], and new onset or  
410 worsening diabetic macular edema with decreased visual acuity [*see Warnings and Precautions*  
411 *(5.6)*].

## 412 **7 DRUG INTERACTIONS**

### 413 **7.1 CYP2C8 Inhibitors and Inducers**

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

## 419 **8 USE IN SPECIFIC POPULATIONS**

### 420 **8.1 Pregnancy**

421 Pregnancy Category C.

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

429 Human Data: Rosiglitazone has been reported to cross the human placenta and be  
430 detectable in fetal tissue. The clinical significance of these findings is unknown. There are no  
431 adequate and well-controlled trials in pregnant women. AVANDIA should be used during  
432 pregnancy only if the potential benefit justifies the potential risk to the fetus.

433 Animal Studies: There was no effect on implantation or the embryo with rosiglitazone  
434 treatment during early pregnancy in rats, but treatment during mid-late gestation was associated  
435 with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed  
436 at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human

437 AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused  
438 placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation  
439 reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible  
440 after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was  
441 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately  
442 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced  
443 the number of uterine implantations and live offspring when juvenile female rats were treated at  
444 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human  
445 AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day  
446 (approximately 4 times human AUC at the maximum recommended daily dose). There was no  
447 effect on pre- or post-natal survival or growth.

## 448 **8.2 Labor and Delivery**

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

## 450 **8.3 Nursing Mothers**

451 Drug-related material was detected in milk from lactating rats. It is not known whether  
452 AVANDIA is excreted in human milk. Because many drugs are excreted in human milk, a  
453 decision should be made whether to discontinue nursing or to discontinue AVANDIA, taking  
454 into account the importance of the drug to the mother.

## 455 **8.4 Pediatric Use**

456 After placebo run-in including diet counseling, children with type 2 diabetes mellitus,  
457 aged 10 to 17 years and with a baseline mean body mass index (BMI) of  $33 \text{ kg/m}^2$ , were  
458 randomized to treatment with 2 mg twice daily of AVANDIA (n = 99) or 500 mg twice daily of  
459 metformin (n = 101) in a 24-week, double-blind clinical trial. As expected, FPG decreased in  
460 patients naïve to diabetes medication (n = 104) and increased in patients withdrawn from prior  
461 medication (usually metformin) (n = 90) during the run-in period. After at least 8 weeks of  
462 treatment, 49% of patients treated with AVANDIA and 55% of metformin-treated patients had  
463 their dose doubled if FPG >126 mg/dL. For the overall intent-to-treat population, at Week 24, the  
464 mean change from baseline in HbA1c was -0.14% with AVANDIA and -0.49% with metformin.  
465 There was an insufficient number of patients in this trial to establish statistically whether these  
466 observed mean treatment effects were similar or different. Treatment effects differed for patients  
467 naïve to therapy with antidiabetic drugs and for patients previously treated with antidiabetic  
468 therapy (Table 6).  
469

470 **Table 6. Week 24 FPG and HbA1c Change From Baseline Last-observation—carried**  
471 **Forward in Children With Baseline HbA1c >6.5%**

Parameter	Naïve Patients		Previously-treated Patients	
	Metformin N = 40	Rosiglitazone N = 45	Metformin N = 43	Rosiglitazone 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%

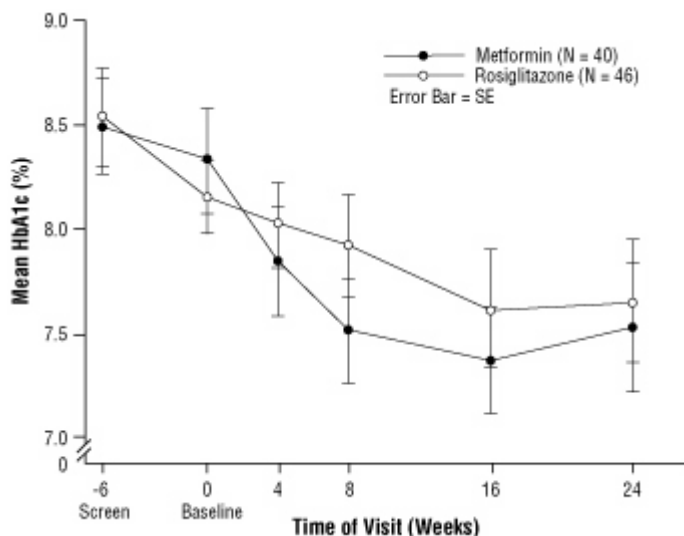
472 <sup>a</sup> Change from baseline means are least squares means adjusting for baseline HbA1c, gender,  
473 and region.

474 <sup>b</sup> Positive values for the difference favor metformin.  
475

476 Treatment differences depended on baseline BMI or weight such that the effects of  
477 AVANDIA and metformin appeared more closely comparable among heavier patients. The  
478 median weight gain was 2.8 kg with rosiglitazone and 0.2 kg with metformin [see *Warnings and*  
479 *Precautions (5.4)*]. Fifty-four percent of patients treated with rosiglitazone and 32% of patients  
480 treated with metformin gained ≥2 kg, and 33% of patients treated with rosiglitazone and 7% of  
481 patients treated with metformin gained ≥5 kg on trial.

482 Adverse events observed in this trial are described in *Adverse Reactions (6.1)*.  
483

484 **Figure 2. Mean HbA1c Over Time in a 24-Week Trial of AVANDIA and Metformin in**  
485 **Pediatric Patients — Drug-naïve Subgroup**



486  
487

### 488 **8.5 Geriatric Use**

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

### 494 **10 OVERDOSAGE**

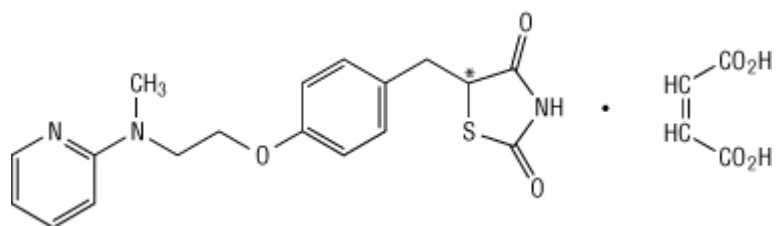
495 Limited data are available with regard to overdosage in humans. In clinical trials in  
496 volunteers, AVANDIA has been administered at single oral doses of up to 20 mg and was well  
497 tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as  
498 dictated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

### 499 **11 DESCRIPTION**

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

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

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



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The molecular formula is C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S•C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>. 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.

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.

520

## 12 CLINICAL PHARMACOLOGY

521

### 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.

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.

540

### 12.2 Pharmacodynamics

541

542

543

544

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

545 (Table 7).

546 Increases in LDL occurred primarily during the first 1 to 2 months of therapy with  
547 AVANDIA and LDL levels remained elevated above baseline throughout the trials. In contrast,  
548 HDL continued to rise over time. As a result, the LDL/HDL ratio peaked after 2 months of  
549 therapy and then appeared to decrease over time. Because of the temporal nature of lipid  
550 changes, the 52-week, glyburide-controlled trial is most pertinent to assess long-term effects on  
551 lipids. At baseline, Week 26, and Week 52, mean LDL/HDL ratios were 3.1, 3.2, and 3.0,  
552 respectively, for AVANDIA 4 mg twice daily. The corresponding values for glyburide were 3.2,  
553 3.1, and 2.9. The differences in change from baseline between AVANDIA and glyburide at  
554 Week 52 were statistically significant.

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

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

560

561 **Table 7. Summary of Mean Lipid Changes in 26-Week, Placebo-controlled and 52-Week,**  
562 **Glyburide-controlled Monotherapy Trials**

Parameter	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>	Week 26	Week 52	Week 26	Week 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%

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

564

565 **12.3 Pharmacokinetics**

566 Maximum plasma concentration ( $C_{\max}$ ) and the area under the curve (AUC) of  
567 rosiglitazone increase in a dose-proportional manner over the therapeutic dose range (Table 8).  
568 The elimination half-life is 3 to 4 hours and is independent of dose.

570 **Table 8. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral**  
571 **Doses (N = 32)**

Parameter	1 mg Fasting	2 mg Fasting	8 mg Fasting	8 mg Fed
AUC <sub>0-inf</sub> (ng.h/mL)	358 (112)	733 (184)	2,971 (730)	2,890 (795)
$C_{\max}$ (ng/mL)	76 (13)	156 (42)	598 (117)	432 (92)
$T_{1/2}$ (h)	3.16 (0.72)	3.15 (0.39)	3.37 (0.63)	3.59 (0.70)
CL/F (L/h)	3.03 (0.87)	2.89 (0.71)	2.85 (0.69)	2.97 (0.81)

572 AUC = area under the curve;  $C_{\max}$  = maximum concentration;  $T_{1/2}$  = terminal half-life;  
573 CL/F = Oral clearance.

574

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

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

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

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

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

593 **Population Pharmacokinetics in Patients With Type 2 Diabetes:** Population  
594 pharmacokinetic analyses from 3 large clinical trials including 642 men and 405 women with

595 type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not  
596 influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral  
597 steady-state volume of distribution (V<sub>ss</sub>/F) were shown to increase with increases in body  
598 weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted  
599 CL/F and V<sub>ss</sub>/F values varied by <1.7-fold and <2.3-fold, respectively. Additionally,  
600 rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about  
601 15%) in female patients.

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

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

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

611 In monotherapy trials, a greater therapeutic response was observed in females; however,  
612 in more obese patients, gender differences were less evident. For a given body mass index  
613 (BMI), females tend to have a greater fat mass than males. Since the molecular target PPAR $\gamma$  is  
614 expressed in adipose tissues, this differentiating characteristic may account, at least in part, for  
615 the greater response to AVANDIA in females. Since therapy should be individualized, no dose  
616 adjustments are necessary based on gender alone.

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

622 Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence  
623 of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of  
624 normal) at baseline [*see Warnings and Precautions (5.5)*].

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

631 **Renal Impairment:** There are no clinically relevant differences in the  
632 pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in  
633 hemodialysis-dependent patients compared with subjects with normal renal function. No dosage  
634 adjustment is therefore required in such patients receiving AVANDIA. Since metformin is

635 contraindicated in patients with renal impairment, coadministration of metformin with  
636 AVANDIA is contraindicated in these patients.

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

## 640 **12.4 Drug-drug Interactions**

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

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

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

656 **Glyburide:** AVANDIA (2 mg twice daily) taken concomitantly with glyburide (3.75 to  
657 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations  
658 in diabetic patients stabilized on glyburide therapy. Repeat doses of AVANDIA (8 mg once  
659 daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and  
660 C<sub>max</sub> of approximately 30%. In Japanese subjects, glyburide AUC and C<sub>max</sub> slightly increased  
661 following coadministration of AVANDIA.

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

666 **Metformin:** Concurrent administration of AVANDIA (2 mg twice daily) and metformin  
667 (500 mg twice daily) in healthy volunteers for 4 days had no effect on the steady-state  
668 pharmacokinetics of either metformin or rosiglitazone.

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

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

674 **Warfarin:** Repeat dosing with AVANDIA had no clinically relevant effect on the steady-

675 state pharmacokinetics of warfarin enantiomers.

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

678 Ranitidine: Pre-treatment with ranitidine (150 mg twice daily for 4 days) did not alter the  
679 pharmacokinetics of either single oral or intravenous doses of rosiglitazone in healthy volunteers.  
680 These results suggest that the absorption of oral rosiglitazone is not altered in conditions  
681 accompanied by increases in gastrointestinal pH.

## 682 **13 NONCLINICAL TOXICOLOGY**

### 683 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

684 Carcinogenesis: A 2-year carcinogenicity study was conducted in Charles River CD-1  
685 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately  
686 12 times human AUC at the maximum recommended human daily dose). Sprague-Dawley rats  
687 were dosed for 2 years by oral gavage at doses of 0.05, 0.3, and 2 mg/kg/day (highest dose  
688 equivalent to approximately 10 and 20 times human AUC at the maximum recommended human  
689 daily dose for male and female rats, respectively).

690 Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of  
691 adipose hyperplasia in the mouse at doses  $\geq 1.5$  mg/kg/day (approximately 2 times human AUC  
692 at the maximum recommended human daily dose). In rats, there was a significant increase in the  
693 incidence of benign adipose tissue tumors (lipomas) at doses  $\geq 0.3$  mg/kg/day (approximately  
694 2 times human AUC at the maximum recommended human daily dose). These proliferative  
695 changes in both species are considered due to the persistent pharmacological overstimulation of  
696 adipose tissue.

697 Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial  
698 assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in  
699 vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about  
700 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic  
701 activation.

702 Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats  
703 given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended  
704 human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility  
705 (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and  
706 estradiol (approximately 20 and 200 times human AUC at the maximum recommended human  
707 daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times  
708 human AUC at the maximum recommended human daily dose). In juvenile rats dosed from  
709 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male  
710 reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in  
711 females (approximately 68 times human AUC at the maximum recommended human daily  
712 dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human  
713 AUC at the maximum recommended human daily dose, respectively) diminished the follicular

714 phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge,  
715 lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears  
716 to be direct inhibition of ovarian steroidogenesis.

### 717 **13.2 Animal Toxicology**

718 Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs  
719 (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at  
720 the maximum recommended human daily dose, respectively). Effects in juvenile rats were  
721 consistent with those seen in adults. Morphometric measurement indicated that there was  
722 hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result  
723 of plasma volume expansion.

## 724 **14 CLINICAL STUDIES**

### 725 **14.1 Monotherapy**

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

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

732 Short-term Clinical Trials: A total of 2,315 patients with type 2 diabetes, previously  
733 treated with diet alone or antidiabetic medication(s), were treated with AVANDIA as  
734 monotherapy in 6 double-blind trials, which included two 26-week, placebo-controlled trials; one  
735 52-week, glyburide-controlled trial; and 3 placebo-controlled, dose-ranging trials of 8 to  
736 12 weeks' duration. Previous antidiabetic medication(s) were withdrawn and patients entered a  
737 2- to 4-week placebo run-in period prior to randomization.

738 Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes  
739 (n = 1,401) with inadequate glycemic control [mean baseline FPG approximately 228 mg/dL  
740 (101 to 425 mg/dL) and mean baseline HbA1c 8.9% (5.2% to 16.2%)], were conducted.  
741 Treatment with AVANDIA produced statistically significant improvements in FPG and HbA1c  
742 compared with baseline and relative to placebo. Data from one of these trials are summarized in  
743 Table 9.

744

745 **Table 9. Glycemic Parameters in a 26-Week, Placebo-controlled Trial**

Parameter	Placebo	AVANDIA		AVANDIA	
	N = 173	4 mg Once Daily N = 180	2 mg Twice Daily N = 186	8 mg Once Daily N = 181	4 mg Twice Daily 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%

746 <sup>a</sup> *P* <0.0001 compared with placebo.

747

748 When administered at the same total daily dose, AVANDIA was generally more effective  
749 in reducing FPG and HbA1c when administered in divided doses twice daily compared with  
750 once-daily doses. However, for HbA1c, the difference between the 4 mg once-daily and 2 mg  
751 twice-daily doses was not statistically significant.

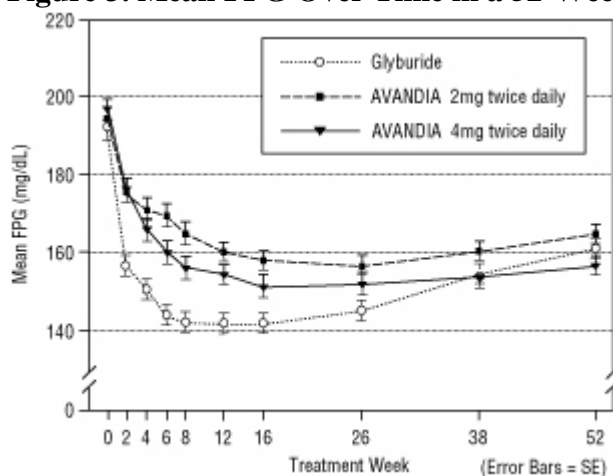
752 **Long-term Clinical Trials:** Long-term maintenance of effect was evaluated in a 52-  
753 week, double-blind, glyburide-controlled trial in patients with type 2 diabetes. Patients were  
754 randomized to treatment with AVANDIA 2 mg twice daily (N = 195) or AVANDIA 4 mg twice  
755 daily (N = 189)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

759 The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a  
760 statistically significant improvement in glycemic control from baseline (Figure 3 and Figure 4).  
761 At the end of Week 52, the reduction from baseline in FPG and HbA1c was -40.8 mg/dL and  
762 -0.53% with AVANDIA 4 mg twice daily; -25.4 mg/dL and -0.27% with AVANDIA 2 mg twice  
763 daily; and -30.0 mg/dL and -0.72% with glyburide. For HbA1c, the difference between  
764 AVANDIA 4 mg twice daily and glyburide was not statistically significant at Week 52. The  
765 initial fall in FPG with glyburide was greater than with AVANDIA; however, this effect was less

766 durable over time. The improvement in glycemic control seen with AVANDIA 4 mg twice daily  
767 at Week 26 was maintained through Week 52 of the trial.

768

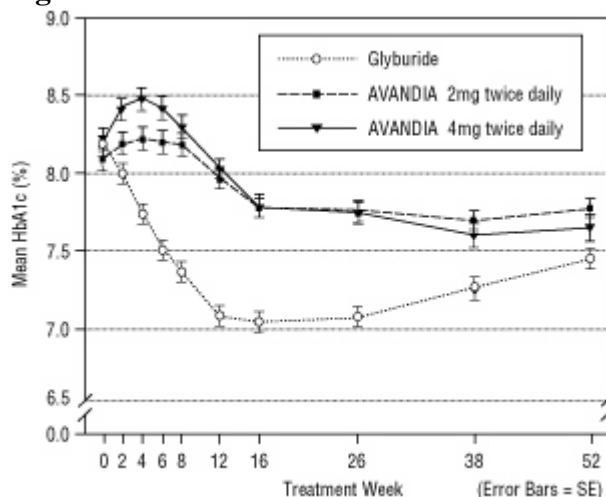
769 **Figure 3. Mean FPG Over Time in a 52-Week, Glyburide-controlled Trial**



770

771

772 **Figure 4. Mean HbA1c Over Time in a 52-Week, Glyburide-controlled Trial**



773

774

775 Hypoglycemia was reported in 12.1% of glyburide-treated patients versus 0.5% (2 mg  
776 twice daily) and 1.6% (4 mg twice daily) of patients treated with AVANDIA. The improvements  
777 in glycemic control were associated with a mean weight gain of 1.75 kg and 2.95 kg for patients  
778 treated with 2 mg and 4 mg twice daily of AVANDIA, respectively, versus 1.9 kg in glyburide-  
779 treated patients. In patients treated with AVANDIA, C-peptide, insulin, pro-insulin, and pro-  
780 insulin split products were significantly reduced in a dose-ordered fashion, compared with an  
781 increase in the glyburide-treated patients.

782

783 A Diabetes Outcome Progression Trial (ADOPT) was a multicenter, double-blind,  
784 controlled trial (N = 4,351) conducted over 4 to 6 years to compare the safety and efficacy of  
AVANDIA, metformin, and glyburide monotherapy in patients recently diagnosed with type 2

785 diabetes mellitus ( $\leq 3$  years) inadequately controlled with diet and exercise. The mean age of  
786 patients in this trial was 57 years and the majority of patients (83%) had no known history of  
787 cardiovascular disease. The mean baseline FPG and HbA1c were 152 mg/dL and 7.4%,  
788 respectively. Patients were randomized to receive either AVANDIA 4 mg once daily, glyburide  
789 2.5 mg once daily, or metformin 500 mg once daily, and doses were titrated to optimal glycemic  
790 control up to a maximum of 4 mg twice daily for AVANDIA, 7.5 mg twice daily for glyburide,  
791 and 1,000 mg twice daily for metformin. The primary efficacy outcome was time to consecutive  
792 FPG  $>180$  mg/dL after at least 6 weeks of treatment at the maximum tolerated dose of study  
793 medication or time to inadequate glycemic control, as determined by an independent  
794 adjudication committee.

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

798 Cardiovascular and adverse event data (including effects on body weight and bone  
799 fracture) from ADOPT for AVANDIA, metformin, and glyburide are described in *Warnings and*  
800 *Precautions* (5.2, 5.4, and 5.7) and *Adverse Reactions* (6.1), respectively. As with all  
801 medications, efficacy results must be considered together with safety information to assess the  
802 potential benefit and risk for an individual patient.

#### 803 **14.2 Combination With Metformin or Sulfonylurea**

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

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

813 In one trial, patients inadequately controlled on 2.5 grams/day of metformin (mean  
814 baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were randomized to receive 4 mg of  
815 AVANDIA once daily, 8 mg of AVANDIA once daily, or placebo in addition to metformin. A  
816 statistically significant improvement in FPG and HbA1c was observed in patients treated with  
817 the combinations of metformin and 4 mg of AVANDIA once daily and 8 mg of AVANDIA once  
818 daily, versus patients continued on metformin alone (Table 10).

819

820 **Table 10. Glycemic Parameters in a 26-Week Combination Trial of AVANDIA Plus**  
821 **Metformin**

Parameter	Metformin N = 113	AVANDIA 4 mg Once Daily + Metformin N = 116	AVANDIA 8 mg Once Daily + Metformin 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%

822 <sup>a</sup> *P* <0.0001 compared with metformin.

823

824 In a second 26-week trial, patients with type 2 diabetes inadequately controlled on  
825 2.5 grams/day of metformin who were randomized to receive the combination of AVANDIA  
826 4 mg twice daily and metformin (N = 105) showed a statistically significant improvement in  
827 glycemic control with a mean treatment effect for FPG of -56 mg/dL and a mean treatment effect  
828 for HbA1c of -0.8% over metformin alone. The combination of metformin and AVANDIA  
829 resulted in lower levels of FPG and HbA1c than either agent alone.

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

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

840 In these trials, the combination of AVANDIA 4 mg or 8 mg daily (administered as

841 single-or twice-daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c  
842 compared with placebo plus sulfonylurea or further up-titration of the sulfonylurea. Table 11  
843 shows pooled data for 8 trials in which AVANDIA added to sulfonylurea was compared with  
844 placebo plus sulfonylurea.  
845

846 **Table 11. Glycemic Parameters in 24- to 26-Week Combination Trials of AVANDIA Plus**  
847 **Sulfonylurea**

<b>Twice-Daily Divided Dosing (5 Trials)</b>	<b>Sulfonylurea N = 397</b>	<b>AVANDIA 2 mg Twice Daily + Sulfonylurea N = 497</b>	<b>Sulfonylurea N = 248</b>	<b>AVANDIA 4 mg Twice Daily + Sulfonylurea N = 346</b>
<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%
<b>Once-Daily Dosing (3 Trials)</b>	<b>Sulfonylurea N = 172</b>	<b>AVANDIA 4 mg Once Daily + Sulfonylurea N = 172</b>	<b>Sulfonylurea N = 173</b>	<b>AVANDIA 8 mg Once Daily + Sulfonylurea N = 176</b>
<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%

848 <sup>a</sup> *P* <0.0001 compared with sulfonylurea alone.

849

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

853 In a 2-year, double-blind trial, elderly patients (aged 59 to 89 years) on half-maximal  
854 sulfonylurea (glipizide 10 mg twice daily) were randomized to the addition of AVANDIA  
855 (n = 115, 4 mg once daily to 8 mg as needed) or to continued up-titration of glipizide (n = 110),  
856 to a maximum of 20 mg twice daily. Mean baseline FPG and HbA1c were 157 mg/dL and  
857 7.72%, respectively, for the arm receiving AVANDIA plus glipizide and 159 mg/dL and 7.65%,  
858 respectively, for the glipizide up-titration arm. Loss of glycemic control (FPG  $\geq$ 180 mg/dL)  
859 occurred in a significantly lower proportion of patients (2%) on AVANDIA plus glipizide  
860 compared with patients in the glipizide up-titration arm (28.7%). About 78% of the patients on  
861 combination therapy completed the 2 years of therapy while only 51% completed on glipizide  
862 monotherapy. The effect of combination therapy on FPG and HbA1c was durable over the 2-year  
863 trial period, with patients achieving a mean of 132 mg/dL for FPG and a mean of 6.98% for  
864 HbA1c compared with no change on the glipizide arm.

### 865 **14.3 Combination With Sulfonylurea Plus Metformin**

866 In two 24- to 26-week, double-blind, placebo-controlled trials designed to assess the  
867 efficacy and safety of AVANDIA in combination with sulfonylurea plus metformin, AVANDIA  
868 4 mg or 8 mg daily, was administered in divided doses twice daily, to patients inadequately  
869 controlled on submaximal (10 mg) and maximal (20 mg) doses of glyburide and maximal dose  
870 of metformin (2 g/day). A statistically significant improvement in FPG and HbA1c was observed  
871 in patients treated with the combinations of sulfonylurea plus metformin and 4 mg of AVANDIA  
872 and 8 mg of AVANDIA versus patients continued on sulfonylurea plus metformin, as shown in  
873 Table 12.

874

875 **Table 12. Glycemic Parameters in a 26-Week Combination Trial of AVANDIA Plus**  
876 **Sulfonylurea and Metformin**

Parameter	Sulfonylurea + Metformin N = 273	AVANDIA 2 mg Twice Daily + Sulfonylurea + Metformin N = 276	AVANDIA 4 mg Twice Daily + Sulfonylurea + Metformin 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%

877 <sup>a</sup> *P* <0.0001 compared with placebo.

878

879 **15 REFERENCES**

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

882 **16 HOW SUPPLIED/STORAGE AND HANDLING**

883 Each pentagonal film-coated TILTAB tablet contains rosiglitazone as the maleate as  
884 follows: 2 mg–pink, debossed with GSK on one side and 2 on the other; 4 mg–orange, debossed  
885 with GSK on one side and 4 on the other; 8 mg–red-brown, debossed with GSK on one side and  
886 8 on the other.

887 2 mg bottles of 60: NDC 0173-0861-18

888 4 mg bottles of 30: NDC 0173-0863-13

889 8 mg bottles of 30: NDC 0173-0864-13

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

892 **17 PATIENT COUNSELING INFORMATION**

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

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

897 Patients should be informed of the following:

- 898 • AVANDIA is not recommended for patients with symptomatic heart failure.
- 899 • A meta-analysis of mostly short-term trials suggested an increased risk for myocardial  
900 infarction with AVANDIA compared with placebo. Data from long-term clinical trials of  
901 AVANDIA versus other antidiabetes agents (metformin or sulfonylureas), including a  
902 cardiovascular outcome trial (RECORD), observed no difference in overall mortality or in  
903 major adverse cardiovascular events (MACE) and its components.
- 904 • AVANDIA is not recommended for patients who are taking insulin.
- 905 • Management of type 2 diabetes should include diet control. Caloric restriction, weight loss,  
906 and exercise are essential for the proper treatment of the diabetic patient because they help  
907 improve insulin sensitivity. This is important not only in the primary treatment of type 2  
908 diabetes, but in maintaining the efficacy of drug therapy.
- 909 • It is important to adhere to dietary instructions and to regularly have blood glucose and  
910 glycosylated hemoglobin tested. It can take 2 weeks to see a reduction in blood glucose and 2  
911 to 3 months to see the full effect of AVANDIA.
- 912 • Blood will be drawn to check their liver function prior to the start of therapy and periodically  
913 thereafter per the clinical judgment of the healthcare professional. Patients with unexplained  
914 symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should  
915 immediately report these symptoms to their physician.
- 916 • Patients who experience an unusually rapid increase in weight or edema or who develop  
917 shortness of breath or other symptoms of heart failure while on AVANDIA should  
918 immediately report these symptoms to their physician.
- 919 • AVANDIA can be taken with or without meals.
- 920 • When using AVANDIA in combination with other hypoglycemic agents, the risk of  
921 hypoglycemia, its symptoms and treatment, and conditions that predispose to its development  
922 should be explained to patients and their family members.
- 923 • Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some  
924 premenopausal anovulatory women. As a result, these patients may be at an increased risk for  
925 pregnancy while taking AVANDIA. Thus, adequate contraception in premenopausal women  
926 should be recommended. This possible effect has not been specifically investigated in  
927 clinical trials so the frequency of this occurrence is not known.

928

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930



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933 Research Triangle Park, NC 27709  
934  
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936  
937 AVD:XXPI

938

## MEDICATION GUIDE

939

### AVANDIA® (ah-VAN-dee-a)

940

### (rosiglitazone maleate) tablets

941

Read this Medication Guide carefully before you start taking AVANDIA and each

942

time you get a refill. There may be new information. This information does not take

943

the place of talking with your doctor about your medical condition or your

944

treatment. If you have any questions about AVANDIA, ask your doctor or

945

pharmacist.

946

#### **What is the most important information I should know about AVANDIA?**

947

#### **AVANDIA may cause serious side effects, including:**

948

##### **New or worse heart failure**

949

- The risk of heart failure may be higher in people who take AVANDIA with insulin.

950

Most people who take insulin should not also take AVANDIA.

951

- AVANDIA can cause your body to keep extra fluid (fluid retention), which leads

952

to swelling (edema) and weight gain. Extra body fluid can make some heart

953

problems worse or lead to heart failure. Heart failure means your heart does not

954

pump blood well enough.

955

- If you have severe heart failure, you cannot start AVANDIA.

956

- If you have heart failure with symptoms (such as shortness of breath or

957

swelling), even if these symptoms are not severe, AVANDIA may not be right for

958

you.

959

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

960

- swelling or fluid retention, especially in the ankles or legs

961

- shortness of breath or trouble breathing, especially when you lie down

962

- an unusually fast increase in weight

963

- unusual tiredness

964

AVANDIA can have other serious side effects. Be sure to read the section below

965

“What are possible side effects of AVANDIA?”

966

#### **What is AVANDIA?**

967

AVANDIA is a prescription medicine used with diet and exercise to treat adults with

968

type 2 (“adult-onset” or “non-insulin dependent”) diabetes mellitus (“high blood

969

sugar”).

970

AVANDIA helps to control high blood sugar. AVANDIA may be used alone or with

971

other diabetes medicines. AVANDIA can help your body respond better to insulin

972

made in your body. AVANDIA does not cause your body to make more insulin.

973

AVANDIA is not for people with type 1 diabetes mellitus or to treat a condition

974 called diabetic ketoacidosis.

975 It is not known if AVANDIA is safe and effective in children younger than 18 years  
976 old.

977 **Who should not take AVANDIA?**

978 Many people with heart failure should not start taking AVANDIA. See “What should  
979 I tell my doctor before taking AVANDIA?”

980 **Do not** take AVANDIA if you are allergic to rosiglitazone or any of the ingredients in  
981 AVANDIA. See the end of this leaflet for a complete list of ingredients in AVANDIA.

982 Symptoms of a severe allergic reaction with AVANDIA may include:

- 983 • swelling of your face, lips, tongue, or throat
- 984 • problems with breathing or swallowing
- 985 • skin rash or itching
- 986 • raised red areas on your skin (hives)
- 987 • blisters on your skin or in your mouth, nose, or eyes
- 988 • peeling of your skin
- 989 • fainting or feeling dizzy
- 990 • very rapid heartbeat

991 **What should I tell my doctor before taking AVANDIA?**

992 Before starting AVANDIA, ask your doctor about what the choices are for diabetes  
993 medicines, and what the expected benefits and possible risks are for you in  
994 particular.

995 Before taking AVANDIA, tell your doctor about all of your medical conditions,  
996 including if you:

- 997 • **have heart problems or heart failure.**
- 998 • **have type 1 (“juvenile”) diabetes or had diabetic ketoacidosis.** These  
999 conditions should be treated with insulin.
- 1000 • **have a type of diabetic eye disease called macular edema** (swelling of the  
1001 back of the eye).
- 1002 • **have liver problems.** Your doctor should do blood tests to check your liver  
1003 before you start taking AVANDIA and during treatment as needed.
- 1004 • **had liver problems while taking REZULIN™ (troglitazone), another**  
1005 **medicine for diabetes.**
- 1006 • **are pregnant or plan to become pregnant.** It is not known if AVANDIA can  
1007 harm your unborn baby. You and your doctor should talk about the best way to  
1008 control your diabetes during pregnancy. If you are a premenopausal woman  
1009 (before the “change of life”) who does not have regular monthly periods,  
1010 AVANDIA may increase your chances of becoming pregnant. Talk to your doctor

1011 about birth control choices while taking AVANDIA. Tell your doctor right away if  
1012 you become pregnant while taking AVANDIA.

1013 • **are breastfeeding or planning to breastfeed.** It is not known if AVANDIA  
1014 passes into breast milk. You and your doctor should decide if you will take  
1015 AVANDIA or breastfeed. You should not do both.

1016 Tell your doctor about all of the medicines you take including prescription and non-  
1017 prescription medicines, vitamins or herbal supplements. AVANDIA and certain other  
1018 medicines can affect each other and may lead to serious side effects including high  
1019 or low blood sugar, or heart problems. Especially tell your doctor if you take:

1020 • **insulin.**  
1021 • **any medicines for high blood pressure, high cholesterol or heart failure,**  
1022 **or for prevention of heart disease or stroke.**

1023 Know the medicines you take. Keep a list of your medicines and show it to your  
1024 doctor and pharmacist before you start a new medicine. They will tell you if it is  
1025 alright to take AVANDIA with other medicines.

#### 1026 **How should I take AVANDIA?**

- 1027 • Take AVANDIA exactly as prescribed. Your doctor will tell you how many tablets  
1028 to take and how often. The usual daily starting dose is 4 mg a day taken one  
1029 time each day or 2 mg taken two times each day. Your doctor may need to  
1030 adjust your dose until your blood sugar is better controlled.
- 1031 • AVANDIA may be prescribed alone or with other diabetes medicines. This will  
1032 depend on how well your blood sugar is controlled.
- 1033 • Take AVANDIA with or without food.
- 1034 • It can take 2 weeks for AVANDIA to start lowering blood sugar. It may take 2 to  
1035 3 months to see the full effect on your blood sugar level.
- 1036 • If you miss a dose of AVANDIA, take it as soon as you remember, unless it is  
1037 time to take your next dose. Take your next dose at the usual time. Do not take  
1038 double doses to make up for a missed dose.
- 1039 • If you take too much AVANDIA, call your doctor or poison control center right  
1040 away.
- 1041 • Test your blood sugar regularly as your doctor tells you.
- 1042 • Diet and exercise can help your body use its blood sugar better. It is important  
1043 to stay on your recommended diet, lose extra weight, and get regular exercise  
1044 while taking AVANDIA.
- 1045 • Your doctor should do blood tests to check your liver before you start AVANDIA  
1046 and during treatment as needed. Your doctor should also do regular blood sugar  
1047 tests (for example, "A1C") to monitor your response to AVANDIA.

1048 **What are possible side effects of AVANDIA?**

1049 **AVANDIA may cause serious side effects including:**

1050 • **New or worse heart failure.** See “What is the most important information I  
1051 should know about AVANDIA?”

1052 • **Heart attack.** AVANDIA may increase the risk of a heart attack. Talk to your  
1053 doctor about what this means to you.

1054 **Symptoms of a heart attack can include the following:**

- 1055 • chest discomfort in the center of your chest that lasts for more than a few  
1056 minutes, or that goes away or comes back
- 1057 • chest discomfort that feels like uncomfortable pressure, squeezing, fullness, or  
1058 pain
- 1059 • pain or discomfort in your arms, back, neck, jaw, or stomach
- 1060 • shortness of breath with or without chest discomfort
- 1061 • breaking out in a cold sweat
- 1062 • nausea or vomiting
- 1063 • feeling lightheaded

1064 **Call your doctor or go to the nearest hospital emergency room right  
1065 away if you think you are having a heart attack.**

1066 • **Swelling (edema).** AVANDIA can cause swelling due to fluid retention. See  
1067 “What is the most important information I should know about AVANDIA?”

1068 • **Weight gain.** AVANDIA can cause weight gain that may be due to fluid  
1069 retention or extra body fat. Weight gain can be a serious problem for people  
1070 with certain conditions including heart problems. See “What is the most  
1071 important information I should know about AVANDIA?”

1072 • **Liver problems.** It is important for your liver to be working normally when you  
1073 take AVANDIA. Your doctor should do blood tests to check your liver before you  
1074 start taking AVANDIA and during treatment as needed. Call your doctor right  
1075 away if you have unexplained symptoms such as:

- 1076 • nausea or vomiting
- 1077 • stomach pain
- 1078 • unusual or unexplained tiredness
- 1079 • loss of appetite
- 1080 • dark urine
- 1081 • yellowing of your skin or the whites of your eyes.

1082 • **Macular edema** (a diabetic eye disease with swelling in the back of the eye).  
1083 Tell your doctor right away if you have any changes in your vision. Your doctor  
1084 should check your eyes regularly. Very rarely, some people have had vision  
1085 changes due to swelling in the back of the eye while taking AVANDIA.

1086 • **Fractures (broken bones),** usually in the hand, upper arm, or foot. Talk to  
1087 your doctor for advice on how to keep your bones healthy.

- 1088 • **Low red blood cell count (anemia).**  
1089 • **Low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness, or  
1090 hunger may mean that your blood sugar is too low. This can happen if you skip  
1091 meals, if you use another medicine that lowers blood sugar, or if you have  
1092 certain medical problems. Call your doctor if low blood sugar levels are a  
1093 problem for you.  
1094 • **Ovulation** (release of egg from an ovary in a woman) leading to pregnancy.  
1095 Ovulation may happen in premenopausal women who do not have regular  
1096 monthly periods. This can increase the chance of pregnancy. See “What should I  
1097 tell my doctor before taking AVANDIA?”

1098 The most common side effects of AVANDIA reported in clinical trials included cold-  
1099 like symptoms and headache.

1100 Call your doctor for medical advice about side effects. You may report side effects  
1101 to FDA at 1-800-FDA-1088.

#### 1102 **How should I store AVANDIA?**

- 1103 • Store AVANDIA at room temperature, 59°F to 86°F (15°C to 30°C). Keep  
1104 AVANDIA in the container it comes in.  
1105 • Safely, throw away AVANDIA that is out of date or no longer needed.  
1106 • Keep AVANDIA and all medicines out of the reach of children.

#### 1107 **General information about AVANDIA**

1108 Medicines are sometimes prescribed for purposes other than those listed in a  
1109 Medication Guide. Do not use AVANDIA for a condition for which it was not  
1110 prescribed. Do not give AVANDIA to other people, even if they have the same  
1111 symptoms you have. It may harm them.

1112 This Medication Guide summarizes important information about AVANDIA. If you  
1113 would like more information, talk with your doctor. You can ask your doctor or  
1114 pharmacist for information about AVANDIA that is written for healthcare  
1115 professionals. You can also find out more about AVANDIA by calling 1-888-825-  
1116 5249.

#### 1117 **What are the ingredients in AVANDIA?**

1118 Active Ingredient: rosiglitazone maleate.

1119 Inactive Ingredients: hypromellose 2910, lactose monohydrate, magnesium  
1120 stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch  
1121 glycolate, titanium dioxide, triacetin, and 1 or more of the following: synthetic red  
1122 and yellow iron oxides and talc.

1123 Always check to make sure that the medicine you are taking is the correct one.

- 1124 AVANDIA tablets are triangles with rounded corners and look like this:  
1125 2 mg – pink with “GSK” on one side and “2” on the other.  
1126 4 mg – orange with “GSK” on one side and “4” on the other.  
1127 8 mg – red-brown with “GSK” on one side and “8” on the other.  
1128 AVANDIA is a registered trademark of the GSK group of companies.  
1129 REZULIN is a trademark of its respective owner and is not a trademark of the GSK  
1130 group of companies. The maker of this brand is not affiliated with and does not  
1131 endorse the GSK group of companies or its products.  
1132 **This Medication Guide has been approved by the U.S. Food and Drug**  
1133 **Administration.**



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1139 AVD: XMG