

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021071

FINAL PRINTED LABELING

AV:L1

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PRESCRIBING INFORMATION

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AVANDIA®

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brand of
rosiglitazone maleate tablets

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DESCRIPTION

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Avandia (rosiglitazone maleate) is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. Avandia is used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes). Avandia improves glycemic control while reducing circulating insulin levels.

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Pharmacological studies in animal models indicate that rosiglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors.

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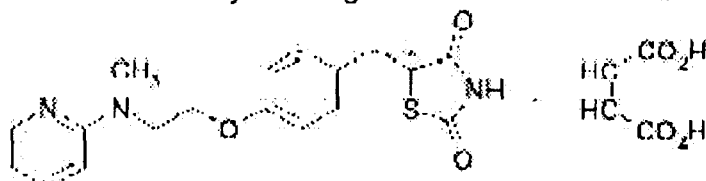
Chemically, rosiglitazone maleate is (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (Z)-2-butenedioate (1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the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

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rosiglitazone maleate

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

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Each pentagonal film-coated Tiltab® tablet contains rosiglitazone maleate equivalent to rosiglitazone, 2 mg, 4 mg, or 8 mg, for oral administration. Inactive ingredients are: hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000,

44

46 sodium starch glycolate, titanium dioxide, triacetin, and one or more of the
47 following: synthetic red and yellow iron oxides and talc.

48 **CLINICAL PHARMACOLOGY**

Mechanism of Action

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

60 Insulin resistance is a common feature characterizing the pathogenesis of type 2
61 diabetes. The antidiabetic activity of rosiglitazone has been demonstrated in
62 animal models of type 2 diabetes in which hyperglycemia and/or impaired
63 glucose tolerance is a consequence of insulin resistance in target tissues.

64 Rosiglitazone reduces blood glucose concentrations and reduces
65 hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse, and fa/fa
66 fatty Zucker rat. Rosiglitazone also prevents the development of overt diabetes
67 in both the db/db mouse and Zucker fa/fa Diabetic Fatty rat models.

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

74

Pharmacokinetics and Drug Metabolism

76 Maximum plasma concentration (C_{max}) and the area under the curve (AUC) of
77 rosiglitazone increase in a dose-proportional manner over the therapeutic dose
78 range (Table 1). The elimination half-life is 3 to 4 hours and is independent of
79 dose.

80

82

Table 1. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral Doses (N=32)

Parameter	1 mg Fasting	2 mg Fasting	8 mg Fasting	8 mg Fed
AUC _{0-inf} [ng.hr./mL]	358 (112)	733 (184)	2971 (730)	2890 (795)
C _{max} [ng/mL]	76 (13)	156 (42)	598 (117)	432 (92)
Half-life [hr.]	3.16 (0.72)	3.15 (0.39)	3.37 (0.63)	3.59 (0.70)
CL/F* [L/hr.]	3.03 (0.87)	2.89 (0.71)	2.85 (0.69)	2.97 (0.81)

* CL/F = Oral Clearance.

84

Absorption

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

92

Distribution

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

98

Metabolism

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

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

110 **Excretion**

112 Following oral or intravenous administration of [¹⁴C]rosiglitazone maleate,
approximately 64% and 23% of the dose was eliminated in the urine and in the
114 feces, respectively. The plasma half-life of [¹⁴C]related material ranged from
103 to 158 hours.

116 **Population Pharmacokinetics in Patients with Type 2 Diabetes**

Population pharmacokinetic analyses from three large clinical trials including
118 642 men and 405 women with type 2 diabetes (aged 35 to 80 years) showed that
the pharmacokinetics of rosiglitazone are not influenced by age, race, smoking,
120 or alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume
of distribution (V_{ss}/F) were shown to increase with increases in body weight.
122 Over the weight range observed in these analyses (50 to 150 kg), the range of
predicted CL/F and V_{ss}/F values varied by <1.7-fold and <2.3-fold, respectively.
124 Additionally, rosiglitazone CL/F was shown to be influenced by both weight and
gender, being lower (about 15%) in female patients.

126

Special Populations

128 **Age:** Results of the population pharmacokinetic analysis (n=716 <65 years;
n=331 ≥65 years) showed that age does not significantly affect the
130 pharmacokinetics of rosiglitazone.

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

136

As monotherapy and in combination with metformin, *Avandia* improved glycemic
138 control in both males and females. In metformin combination studies, efficacy
was demonstrated with no gender differences in glycemic response.

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In monotherapy studies, a greater therapeutic response was observed in
142 females; however, in more obese patients, gender differences were less evident.
For a given body mass index (BMI), females tend to have a greater fat mass
144 than males. Since the molecular target PPAR_γ is expressed in adipose tissues,
this differentiating characteristic may account, at least in part, for the greater
146 response to *Avandia* in females. Since therapy should be individualized, no
dose adjustments are necessary based on gender alone.

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Hepatic Impairment: Unbound oral clearance of rosiglitazone was significantly
150 lower in patients with moderate to severe liver disease (Child-Pugh Class B/C)
compared to healthy subjects. As a result, unbound C_{max} and AUC_{0-inf} were
152 increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was

154 about 2 hours longer in patients with liver disease, compared to healthy
156 subjects.

156 Therapy with *Avandia* should not be initiated if the patient exhibits clinical
158 evidence of active liver disease or increased serum transaminase levels (ALT
158 >2.5X upper limit of normal) at baseline (see PRECAUTIONS, Hepatic Effects).

160 **Renal Impairment:** There are no clinically relevant differences in the
162 pharmacokinetics of rosiglitazone in patients with mild to severe renal
162 impairment or in hemodialysis-dependent patients compared to subjects with
164 normal renal function. No dosage adjustment is therefore required in such
164 patients receiving *Avandia*. Since metformin is contraindicated in patients with
166 renal impairment, co-administration of metformin with *Avandia* is contraindicated
166 in these patients.

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

172 **Pediatric Use:** The safety and effectiveness of *Avandia* in pediatric patients
174 have not been established.

174 **Pharmacodynamics and Clinical Effects**

176 In clinical studies, treatment with *Avandia* resulted in an improvement in
176 glycemic control, as measured by fasting plasma glucose (FPG) and hemoglobin
178 A1c (HbA1c), with a concurrent reduction in insulin and C-peptide. Postprandial
178 glucose and insulin were also reduced. This is consistent with the mechanism of
180 action of *Avandia* as an insulin sensitizer. The improvement in glycemic control
180 was durable, with maintenance of effect for 52 weeks. The maximum
182 recommended daily dose is 8 mg. Dose-ranging studies suggested that no
182 additional benefit was obtained with a total daily dose of 12 mg.

184 The addition of *Avandia* to metformin resulted in significant reductions in
186 hyperglycemia compared to either of the agents alone. These results are
186 consistent with a synergistic effect of *Avandia* plus metformin combination
188 therapy on glycemic control.

190 Reduction in hyperglycemia was associated with increases in weight. In the 26-
190 week clinical trials, the mean weight gain in patients treated with *Avandia* was
192 1.2 kg (4 mg daily) and 3.5 kg (8 mg daily) when administered as monotherapy
192 and 0.7 kg (4 mg daily) and 2.3 kg (8 mg daily) when administered in
194 combination with metformin. A mean weight loss of about 1 kg was seen for both
194 placebo and metformin alone in these studies. In the 52-week glyburide-
196 controlled study, there was a mean weight gain of 1.75 kg and 2.95 kg for

198 patients treated with 4 mg and 8 mg of *Avandia* daily, respectively, versus 1.9 kg
in glyburide-treated patients.

200 Patients with lipid abnormalities were not excluded from clinical trials of *Avandia*.
202 In all 26-week controlled trials, across the recommended dose range, *Avandia* as
204 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 (Table 2).

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

216 The pattern of LDL and HDL changes following therapy with *Avandia* in
218 combination with metformin were generally similar to those seen with *Avandia* in
monotherapy.

220 The changes in triglycerides during therapy with *Avandia* were variable and were
222 generally not statistically different from placebo or glyburide controls.

224

Table 2. Summary of Mean Lipid Changes in 26-Week Placebo-Controlled and 52-Week Glyburide-Controlled Monotherapy Studies

	Placebo-controlled Studies Week 26			Glyburide-controlled Study Week 26 and Week 52			
	Placebo	Avandia		Glyburide titration		Avandia 8 mg	
		4 mg daily*	8 mg daily*	Wk 26	Wk 52	Wk 26	Wk 52
Free Fatty Acids							
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%
LDL							
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%
HDL							
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%

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* once daily and twice daily dosing groups were combined.

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Clinical Studies Monotherapy

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A total of 2315 patients with type 2 diabetes, previously treated with diet alone or antidiabetic medication(s), were treated with *Avandia* as monotherapy in six

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double-blind studies, which included two 26-week placebo-controlled studies, one 52-week glyburide-controlled study, and three placebo-controlled dose-

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ranging studies of 8 to 12 weeks duration. Previous antidiabetic medication(s) were withdrawn and patients entered a 2 to 4 week placebo run-in period prior to

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randomization.

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Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes with inadequate glycemic control (mean baseline FPG approximately

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228 mg/dL and mean baseline HbA1c 8.9%), were conducted. Treatment with *Avandia* produced statistically significant improvements in FPG and HbA1c

242

compared to baseline and relative to placebo (Table 3).

Table 3. Glycemic Parameters in Two 26-Week Placebo-Controlled Trials

	Placebo	Avandia		Avandia	
		2 mg twice daily	2 mg twice daily	4 mg twice daily	
STUDY A					
N	158	166		169	
FPG (mg/dL)					
Baseline (mean)	229	227		220	
Change from baseline (mean)	19	-38		-54	
Difference from placebo (adjusted mean)		-58*		-76*	
Responders (≥ 30 mg/dL decrease from baseline)	16%	54%		64%	
HbA1c (%)					
Baseline (mean)	9.0	9.0		8.8	
Change from baseline (mean)	0.9	-0.3		-0.6	
Difference from placebo (adjusted mean)		-1.2*		-1.5*	
Responders ($\geq 0.7\%$ decrease from baseline)	6%	40%		42%	
	Placebo	Avandia 4 mg once daily	Avandia 2 mg twice daily	Avandia 8 mg once daily	Avandia 4 mg twice daily
STUDY B					
N	173	180	186	181	187
FPG (mg/dL)					
Baseline (mean)	225	229	225	228	228
Change from baseline (mean)	8	-25	-35	-42	-55
Difference from placebo (adjusted mean)	-	-31*	-43*	-49*	-62*
Responders (≥ 30 mg/dL decrease from baseline)	19%	45%	54%	58%	70%
HbA1c (%)					
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*	-0.9*	-1.1*	-1.5*
Responders ($\geq 0.7\%$ decrease from baseline)	9%	28%	29%	39%	54%

244

* <0.0001 compared to placebo.

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When administered at the same total daily dose, *Avandia* was generally more effective in reducing FPG and HbA1c when administered in divided doses twice daily compared to once daily doses. However, for HbA1c, the difference

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250 between the 4 mg once daily and 2 mg twice daily doses was not statistically
251 significant.

252 Long-term maintenance of effect was evaluated in a 52-week, double-blind,
253 glyburide-controlled trial in patients with type 2 diabetes. Patients were
254 randomized to treatment with *Avandia* 2 mg twice daily (N=195) or *Avandia* 4 mg
255 twice daily (N=189) or glyburide (N=202) for 52 weeks. Patients receiving
256 glyburide were given an initial dosage of either 2.5 mg/day or 5.0 mg/day. The
257 dosage was then titrated in 2.5 mg/day increments over the next 12 weeks, to a
258 maximum dosage of 15.0 mg/day in order to optimize glycemic control.
259 Thereafter the glyburide dose was kept constant.

260
261 The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a
262 statistically significant improvement in glycemic control from baseline (Figures 1
263 and 2). At the end of week 52, the reduction from baseline in FPG and HbA1c
264 was -40.8 mg/dL and -0.53% with *Avandia* 4 mg twice daily; -25.4 mg/dL and -
265 0.27% with *Avandia* 2 mg twice daily; and -30.0 mg/dL and -0.72% with
266 glyburide. For HbA1c, the difference between *Avandia* 4 mg twice daily and
267 glyburide was not statistically significant at week 52. The initial fall in FPG with
268 glyburide was greater than with *Avandia*; however, this effect was less durable
269 over time. The improvement in glycemic control seen with *Avandia* 4 mg twice
270 daily at week 26 was maintained through week 52 of the study.

Figure 1. Mean FPG Over Time in a 52-Week Glyburide-Controlled Study

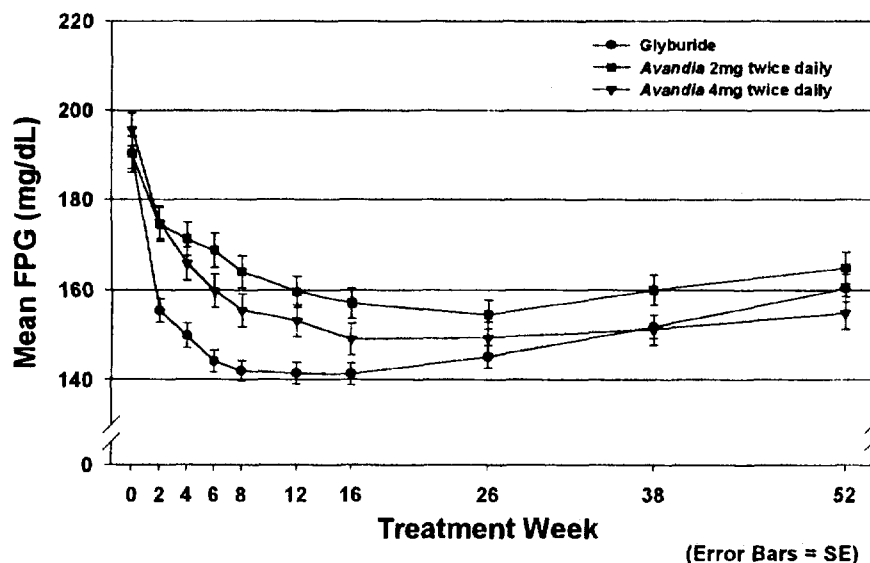
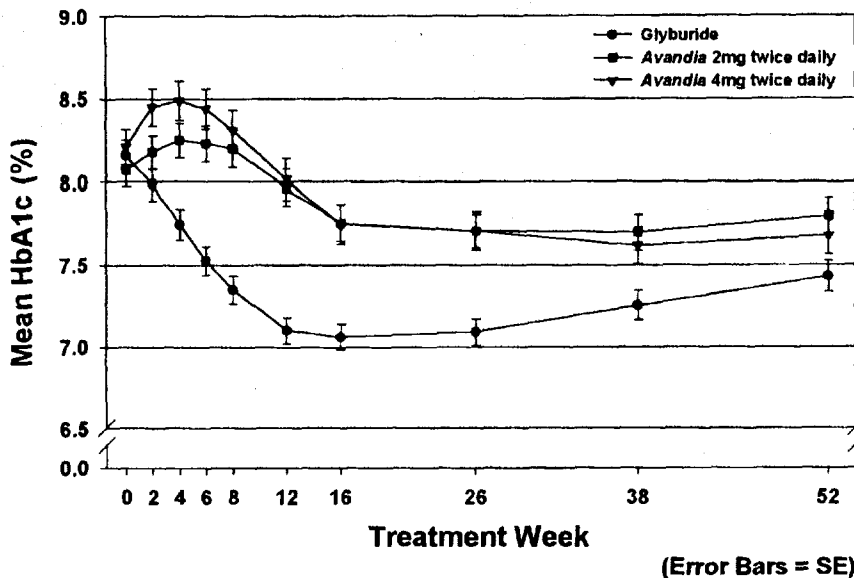


Figure 2. Mean HbA1c Over Time in a 52-Week Glyburide-Controlled Study



274 Hypoglycemia was reported in 12.1% of glyburide-treated patients versus 0.5%
 276 (2 mg twice daily) and 1.6% (4 mg twice daily) of patients treated with *Avandia*.
 278 The improvements in glycemic control were associated with a mean weight gain
 280 of 1.75 kg and 2.95 kg for patients treated with 2 mg and 4 mg twice daily of
 282 *Avandia*, respectively versus 1.9 kg in glyburide-treated patients. In patients
 284 treated with *Avandia*, C-peptide, insulin, pro-insulin, and pro-insulin split
 286 products were significantly reduced in a dose-ordered fashion, compared to an
 288 increase in the glyburide-treated patients.

282 **Combination with Metformin**

284 A total of 670 patients with type 2 diabetes participated in two 26-week,
 286 randomized, double-blind, placebo/active-controlled studies designed to assess
 288 the efficacy of *Avandia* in combination with metformin. *Avandia*, administered in
 either once daily or twice daily dosing regimens, was added to the therapy of
 patients who were inadequately controlled on a maximum dose (2.5 grams/day)
 of metformin.

290 In one study, patients inadequately controlled on 2.5 grams/day of metformin
 292 (mean baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were
 294 randomized to receive *Avandia* 4 mg once daily, *Avandia* 8 mg once daily, or
 296 placebo in addition to metformin. A statistically significant improvement in FPG
 and HbA1c was observed in patients treated with the combinations of metformin
 and *Avandia* 4 mg once daily and *Avandia* 8 mg once daily, versus patients
 continued on metformin alone (Table 4).

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Table 4. Glycemic Parameters in a 26-Week Combination Study

	Metformin	<i>Avandia</i> 4 mg once daily + metformin	<i>Avandia</i> 8 mg once daily + metformin
N	113	116	110
FPG (mg/dL)			
Baseline (mean)	214	215	220
Change from baseline (mean)	6	-33	-48
Difference from placebo (adjusted mean)		-40*	-53*
Responders (≥30 mg/dL decrease from baseline)	20%	45%	61%
HbA1c (%)			
Baseline (mean)	8.6	8.9	8.9
Change from baseline (mean)	0.5	-0.6	-0.8
Difference from placebo (adjusted mean)		-1.0*	-1.2*
Responders (≥0.7% decrease from baseline)	11%	45%	52%

*<0.0001 compared to metformin.

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

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

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314 **INDICATIONS AND USAGE**

Avandia is indicated as monotherapy as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

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Avandia is also indicated for use in combination with metformin when diet, exercise, and *Avandia* alone or diet, exercise, and metformin alone do not result in adequate glycemic control in patients with type 2 diabetes. For patients inadequately controlled with a maximum dose of metformin, *Avandia* should be added to, rather than substituted for, metformin.

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

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CONTRAINDICATIONS

332 *Avandia* is contraindicated in patients with known hypersensitivity to this product
or any of its components.

334

PRECAUTIONS

336 General

Due to its mechanism of action, *Avandia* is active only in the presence of insulin.
338 Therefore, *Avandia* should not be used in patients with type 1 diabetes or for the
treatment of diabetic ketoacidosis.

340

Ovulation: *Avandia*, like other thiazolidinediones, may result in resumption of
342 ovulation in premenopausal, anovulatory women with insulin resistance. **As a
consequence of their improved insulin sensitivity, these patients may be at
344 risk for pregnancy if adequate contraception is not used.**

346 Although hormonal imbalance has been seen in preclinical studies (see
Carcinogenesis, Mutagenesis, Impairment of Fertility), the clinical significance of
348 this finding is not known. If unexpected menstrual dysfunction occurs, the
benefits of continued therapy with *Avandia* should be reviewed.

350

Hematologic: Across all controlled clinical studies, decreases in hemoglobin
352 and hematocrit (mean decreases in individual studies ≤ 1.0 gram/dL and $\leq 3.3\%$,
respectively) were observed for both *Avandia* alone and in combination with
354 metformin. The changes occurred primarily during the first 4 to 8 weeks of
therapy and remained relatively constant thereafter. White blood cell counts
356 also decreased slightly in patients treated with *Avandia*. The observed changes
may be related to the increased plasma volume observed with treatment with
358 *Avandia* and have not been associated with any significant hematologic clinical
effects (see ADVERSE REACTIONS, Laboratory Abnormalities).

360

Edema: *Avandia* should be used with caution in patients with edema. In a
362 clinical study in healthy volunteers who received *Avandia* 8 mg once daily for 8
weeks, there was a statistically significant increase in median plasma volume
364 (1.8 mL/kg) compared to placebo.

366 In controlled clinical trials of patients with type 2 diabetes, mild to moderate
edema was reported in patients treated with *Avandia* (see ADVERSE
368 REACTIONS).

Use in Patients with Heart Failure: In preclinical studies, thiazolidinediones,
370 including rosiglitazone, cause plasma volume expansion and pre-load-induced
cardiac hypertrophy. Two ongoing echocardiography studies in patients with
372 type 2 diabetes (a 52-week study with *Avandia* 4 mg twice daily [n=86] and a 26-
week study with 8 mg once daily [n=90]), have shown no deleterious alteration in
374

376 cardiac structure or function. These studies were designed to detect a change
in left ventricular mass of 10% or more.

378 Patients with New York Heart Association (NYHA) Class 3 and 4 cardiac status
were not studied during the clinical trials. *Avandia* is not indicated in patients
380 with NYHA Class 3 and 4 cardiac status unless the expected benefit is judged to
outweigh the potential risk.

382 **Hepatic Effects:** Another drug of the thiazolidinedione class, troglitazone, has
384 been associated with idiosyncratic hepatotoxicity, and very rare cases of liver
failure, liver transplants, and death have been reported during postmarketing
386 clinical use. In pre-approval controlled clinical trials in patients with type 2
diabetes, troglitazone was more frequently associated with clinically significant
388 elevations of hepatic enzymes (ALT >3X upper limit of normal) compared to
placebo, and very rare cases of reversible jaundice were reported.

390 In clinical studies in 4598 patients treated with *Avandia*, encompassing
392 approximately 3600 patient years of exposure, there was no evidence of drug-
induced hepatotoxicity or elevation of ALT levels.

394 In controlled trials, 0.2% of patients treated with *Avandia* had elevations in ALT
396 >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active
comparators. The ALT elevations in patients treated with *Avandia* were
398 reversible and were not clearly causally related to therapy with *Avandia*.

400 Although available clinical data show no evidence of *Avandia* induced
hepatotoxicity or ALT elevations, rosiglitazone is structurally very similar to
402 troglitazone, which has been associated with idiosyncratic hepatotoxicity and
rare cases of liver failure, liver transplants, and death. Pending the availability
404 of the results of additional large, long-term controlled clinical trials and
postmarketing safety data following wide clinical use of *Avandia* to more fully
406 define its hepatic safety profile, it is recommended that patients treated with
Avandia undergo periodic monitoring of liver enzymes. Liver enzymes should be
408 checked prior to the initiation of therapy with *Avandia* in all patients. Therapy
with *Avandia* should not be initiated in patients with increased baseline liver
410 enzyme levels (ALT >2.5X upper limit of normal). In patients with normal
baseline liver enzymes, following initiation of therapy with *Avandia*, it is
412 recommended that liver enzymes be monitored every two months for the first
twelve months, and periodically thereafter. Patients with mildly elevated liver
414 enzymes (ALT levels one to 2.5X upper limit of normal) at baseline or during
therapy with *Avandia* should be evaluated to determine the cause of the liver
416 enzyme elevation. Initiation of, or continuation of, therapy with *Avandia* in
patients with mild liver enzyme elevations should proceed with caution and
418 include appropriate close clinical follow-up, including more frequent liver enzyme
monitoring, to determine if the liver enzyme elevations resolve or worsen. If at

420 any time ALT levels increase to >3X upper limit of normal in patients on therapy
with *Avandia*, liver enzyme levels should be rechecked as soon as possible. If
422 ALT levels remain >3X the upper limit of normal, therapy with *Avandia* should be
discontinued.

424
426 There are no data available to evaluate the safety of *Avandia* in patients who
experience liver abnormalities, hepatic dysfunction, or jaundice while on
troglitazone. *Avandia* should not be used in patients who experienced jaundice
428 while taking troglitazone. For patients with normal hepatic enzymes who are
switched from troglitazone to *Avandia*, a one week washout is recommended
430 before starting therapy with *Avandia*.

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

438

Laboratory Tests

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

442

Liver enzyme monitoring is recommended prior to initiation of therapy with
444 *Avandia* in all patients and periodically thereafter (See PRECAUTIONS, Hepatic
Effects and ADVERSE REACTIONS, Serum Transaminase Levels).

446

Information for Patients

448 Patients should be informed of the following:

450 Management of type 2 diabetes should include diet control. Caloric restriction,
weight loss, and exercise are essential for the proper treatment of the diabetic
452 patient because they help improve insulin sensitivity. This is important not only
in the primary treatment of type 2 diabetes, but in maintaining the efficacy of
drug therapy.

454

456 It is important to adhere to dietary instructions and to regularly have blood
glucose and glycosylated hemoglobin tested. Patients should be informed that
blood will be drawn to check their liver function prior to the start of therapy and
458 every two months for the first twelve months, and periodically thereafter.

460 Patients with unexplained symptoms of nausea, vomiting, abdominal pain,
fatigue, anorexia, or dark urine should immediately report these symptoms to
their physician.

462

464 *Avandia* can be taken with or without meals.

466 Use of *Avandia* may cause resumption of ovulation in premenopausal,
anovulatory women with insulin resistance. Therefore, contraceptive measures
468 may need to be considered.

468 **Drug Interactions**

470 ***Drugs Metabolized by Cytochrome P₄₅₀***

472 *In vitro* drug metabolism studies suggest that rosiglitazone does not inhibit any
of the major P₄₅₀ enzymes at clinically relevant concentrations. *In vitro* data
474 demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to
a lesser extent, 2C9.

476 *Avandia* (4 mg twice daily) was shown to have no clinically relevant effect on the
pharmacokinetics of nifedipine and oral contraceptives (ethinylestradiol and
478 norethindrone), which are predominantly metabolized by CYP3A4.

480 *Glyburide: Avandia* (2 mg twice daily) taken concomitantly with glyburide (3.75 to
10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma
482 glucose concentrations in diabetic patients stabilized on glyburide therapy.

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

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

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

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

498
500 *Ethanol:* A single administration of a moderate amount of alcohol did not
increase the risk of acute hypoglycemia in type 2 diabetes mellitus patients
502 treated with *Avandia*.

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

508

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

526
Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the *in vitro*
528 bacterial assays for gene mutation, the *in vitro* chromosome aberration test in
human lymphocytes, the *in vivo* mouse micronucleus test, and the *in vivo/in vitro*
530 rat UDS assay. There was a small (about 2-fold) increase in mutation in the *in
vitro* mouse lymphoma assay in the presence of metabolic activation.

532
Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male
534 rats given up to 40 mg/kg/day (approximately 116 times human AUC at the
maximum recommended human daily dose). Rosiglitazone altered estrous
536 cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in
association with lower plasma levels of progesterone and estradiol
538 (approximately 20 and 200 times human AUC at the maximum recommended
human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day
540 (approximately 3 times human AUC at the maximum recommended human daily
dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and
542 15 times human AUC at the maximum recommended human daily dose,
respectively) diminished the follicular phase rise in serum estradiol with
544 consequential reduction in the luteinizing hormone surge, lower luteal phase
progesterone levels, and amenorrhea. The mechanism for these effects
546 appears to be direct inhibition of ovarian steroidogenesis.

548 **Animal Toxicology**

Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and
550 dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2
times human AUC at the maximum recommended human daily dose,
552 respectively). Morphometric measurement indicated that there was hypertrophy
in cardiac ventricular tissues, which may be due to increased heart work as a
554 result of plasma volume expansion.

556 **Pregnancy**

Pregnancy Category C

558 There was no effect on implantation or the embryo with rosiglitazone treatment
560 during early pregnancy in rats, but treatment during mid-late gestation was
562 associated with fetal death and growth retardation in both rats and rabbits.
564 Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in
566 rabbits (approximately 20 and 75 times human AUC at the maximum
568 recommended human daily dose, respectively). Rosiglitazone caused placental
570 pathology in rats (3 mg/kg/day). Treatment of rats during gestation through
572 lactation reduced litter size, neonatal viability, and postnatal growth, with growth
574 retardation reversible after puberty. For effects on the placenta, embryo/fetus,
576 and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in
578 rabbits. These no-effect levels are approximately 4 times human AUC at the
580 maximum recommended human daily dose.

570 There are no adequate and well-controlled studies in pregnant women. *Avandia*
572 should not be used during pregnancy unless the potential benefit justifies the
574 potential risk to the fetus.

574 Because current information strongly suggests that abnormal blood glucose
576 levels during pregnancy are associated with a higher incidence of congenital
578 anomalies as well as increased neonatal morbidity and mortality, most experts
580 recommend that insulin be used during pregnancy to maintain blood glucose
582 levels as close to normal as possible.

580 **Labor and Delivery**

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

584 **Nursing Mothers**

586 Drug related material was detected in milk from lactating rats. It is not known
588 whether *Avandia* is excreted in human milk. Because many drugs are excreted
in human milk, *Avandia* should not be administered to a nursing woman.

588 **ADVERSE REACTIONS**

590 In clinical trials, approximately 4600 patients with type 2 diabetes have been
592 treated with *Avandia*; 3300 patients were treated for 6 months or longer and
2000 patients were treated for 12 months or longer.

594 The incidence and types of adverse events reported in clinical trials of *Avandia*
596 as monotherapy are shown in Table 5.

Table 5: Adverse Events ($\geq 5\%$ in Any Treatment Group) Reported by Patients in Double-blind Clinical Trials with *Avandia* as Monotherapy

Preferred Term	<i>Avandia</i>	Placebo	Metformin	Sulfonylureas
	Monotherapy			
	N = 2526	N = 601	N = 225	N = 626
	%	%	%	%
Upper respiratory tract infection	9.9	8.7	8.9	7.3
Injury	7.6	4.3	7.6	6.1
Headache	5.9	5.0	8.9	5.4
Back pain	4.0	3.8	4.0	5.0
Hyperglycemia	3.9	5.7	4.4	8.1
Fatigue	3.6	5.0	4.0	1.9
Sinusitis	3.2	4.5	5.3	3.0
Diarrhea	2.3	3.3	15.6	3.0
Hypoglycemia	0.6	0.2	1.3	5.9

* Includes patients receiving glyburide (N=514), glimepiride (N=91) or glipizide (N=21).

600 There were a small number of patients treated with *Avandia* who had adverse
 602 events of anemia and edema. Overall, these events were generally mild to
 moderate in severity and usually did not require discontinuation of treatment with
Avandia.

604

In double-blind studies, anemia was reported in 1.9% of patients receiving
 606 *Avandia* compared to 0.7% on placebo, 0.6% on sulfonylureas and 2.2% on
 metformin. Edema was reported in 4.8% of patients receiving *Avandia* compared
 608 to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2 % on metformin. Overall,
 the types of adverse experiences reported when *Avandia* was used in
 610 combination with metformin were similar to those during monotherapy with
Avandia. Reports of anemia (7.1%) were greater in patients treated with a
 612 combination of *Avandia* and metformin compared to monotherapy with *Avandia*.

614 Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the
 metformin combination clinical trials may have contributed to the higher reporting
 616 rate of anemia in these studies (see Laboratory Abnormalities, Hematologic).

618 **Laboratory Abnormalities**

Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a
 620 dose-related fashion in patients treated with *Avandia* (mean decreases in
 individual studies up to 1.0 gram/dL hemoglobin and up to 3.3% hematocrit).
 622 The time course and magnitude of decreases were similar in patients treated
 with a combination of *Avandia* and metformin or monotherapy. Pre-treatment

624 levels of hemoglobin and hematocrit were lower in patients in metformin
626 combination studies and may have contributed to the higher reporting rate of
628 anemia. White blood cell counts also decreased slightly in patients treated with
Avandia. Decreases in hematologic parameters may be related to increased
plasma volume observed with treatment with *Avandia*.

630 **Lipids:** Changes in serum lipids have been observed following treatment with
632 *Avandia* (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical
Effects).

634 **Serum Transaminase Levels:** In clinical studies in 4598 patients treated with
636 *Avandia* encompassing approximately 3600 patient years of exposure, there was
no evidence of drug-induced hepatotoxicity or elevated ALT levels.

638 In controlled trials, 0.2% of patients treated with *Avandia* had reversible
640 elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo
and 0.5% on active comparators. Hyperbilirubinemia was found in 0.3% of
642 patients treated with *Avandia* compared with 0.9% treated with placebo and 1%
in patients treated with active comparators.

644 In the clinical program including long-term, open-label experience, the rate per
646 100 patient years exposure of ALT increase to >3X the upper limit of normal was
0.35 for patients treated with *Avandia*, 0.59 for placebo-treated patients, and
0.78 for patients treated with active comparator agents.

648 In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions
650 leading to hepatic failure (see PRECAUTIONS, Hepatic Effects).

652 **DOSAGE AND ADMINISTRATION**

The management of antidiabetic therapy should be individualized.

654

Monotherapy

656 The usual starting dose of *Avandia* is 4 mg administered either as a single dose
658 once daily or in divided doses twice daily. For patients who respond
inadequately following 12 weeks of treatment as determined by reduction in
FPG, the dose may be increased to 8 mg administered as a single dose once
660 daily or in divided doses twice daily. Reductions in glycemic parameters by
dose and regimen are described under CLINICAL PHARMACOLOGY, Clinical
662 Efficacy. In clinical trials, the 4 mg twice daily regimen resulted in the greatest
reduction in FPG and HbA1c.

664

Combination Therapy with Metformin

666 The usual starting dose of *Avandia* in combination with metformin is 4 mg
administered as either a single dose once daily or in divided doses twice daily.
668 The dose of *Avandia* may be increased to 8 mg/day following 12 weeks of

670 therapy if there is insufficient reduction in FPG. *Avandia* may be administered
672 as a single daily dose in the morning, or divided and administered in the morning
and evening.

674 *Avandia* may be taken with or without food.

676 No dosage adjustments are required for the elderly.

678 No dosage adjustment is necessary when *Avandia* is used as monotherapy in
680 patients with renal impairment. Since metformin is contraindicated in such
patients, concomitant administration of metformin and *Avandia* is also
contraindicated in patients with renal impairment.

682 Therapy with *Avandia* should not be initiated if the patient exhibits clinical
684 evidence of active liver disease or increased serum transaminase levels (ALT
>2.5 times the upper limit of normal at start of therapy (See PRECAUTIONS,
Hepatic Effects and CLINICAL PHARMACOLOGY, Hepatic Impairment). Liver
686 enzyme monitoring is recommended in all patients prior to initiation of therapy
with *Avandia* and periodically thereafter (See PRECAUTIONS, *Hepatic Effects*).

688 There are no data on the use of *Avandia* in patients under 18 years of age;
690 therefore, use of *Avandia* in pediatric patients is not recommended.

692 **OVERDOSAGE**

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

698

HOW SUPPLIED

700 **Tablets:** Each pentagonal film-coated Tiltab[®] tablet contains rosiglitazone as
the maleate as follows: 2 mg—pink, debossed with SB on one side and 2 on the
702 other; 4 mg—orange, debossed with SB on one side and 4 on the other; 8 mg—
red-brown, debossed with SB on one side and 8 on the other.

704

2 mg bottles of 30: NDC 0029-3158-13

706 2 mg bottles of 60: NDC 0029-3158-18

2 mg bottles of 100: NDC 0029-3158-20

708 2 mg bottles of 500: NDC 0029-3158-25

2 mg SUP 100s: NDC 0029-3158-21

710

4 mg bottles of 30: NDC 0029-3159-13

712 4 mg bottles of 60: NDC 0029-3159-18

4 mg bottles of 100: NDC 0029-3159-20

714 4 mg bottles of 500: NDC 0029-3159-25
4 mg SUP 100s: NDC 0029-3159-21

716 8 mg bottles of 30: NDC 0029-3160-13
718 8 mg bottles of 100: NDC 0029-3160-20
8 mg bottles of 500: NDC 0029-3160-25
720 8 mg SUP 100s: NDC 0029-3160-21

722 **STORAGE**

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

726 DATE OF ISSUANCE MONTH YEAR
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728 **SmithKline Beecham Pharmaceuticals**
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732 Rx only

734 **AV:L1**