

PRESCRIBING INFORMATION

AVANDAMET[®]

(rosiglitazone maleate and metformin hydrochloride)

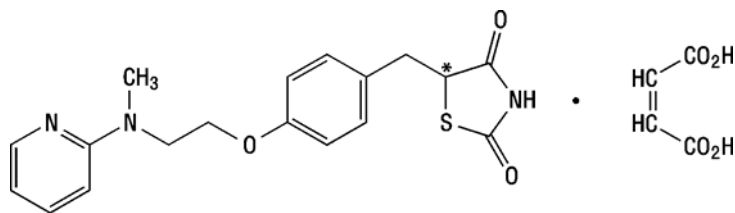
Tablets

DESCRIPTION

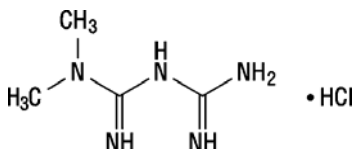
AVANDAMET (rosiglitazone maleate and metformin HCl) tablets contain 2 oral antihyperglycemic drugs used in the management of type 2 diabetes: Rosiglitazone maleate and metformin hydrochloride.

Rosiglitazone maleate is an oral antidiabetic agent, which acts primarily by increasing insulin sensitivity. Rosiglitazone improves glycemic control while reducing circulating insulin levels. Pharmacologic 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 α -glucosidase inhibitors.

Chemically, rosiglitazone maleate is (\pm)-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 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 pK_a 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. The structural formula of rosiglitazone maleate is:



Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula of metformin hydrochloride is:



33 AVANDAMET is available for oral administration as tablets containing rosiglitazone maleate
34 and metformin hydrochloride equivalent to: 2 mg rosiglitazone with 500 mg metformin
35 hydrochloride (2 mg/500 mg), 4 mg rosiglitazone with 500 mg metformin hydrochloride
36 (4 mg/500 mg), 2 mg rosiglitazone with 1,000 mg metformin hydrochloride (2 mg/1,000 mg),
37 and 4 mg rosiglitazone with 1,000 mg metformin hydrochloride (4 mg/1,000 mg). In addition,
38 each tablet contains the following inactive ingredients: Hypromellose 2910, lactose
39 monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, povidone
40 29-32, sodium starch glycolate, titanium dioxide, and 1 or more of the following: Red and yellow
41 iron oxides.

42 **CLINICAL PHARMACOLOGY**

43 **Mechanism of Action**

44 **AVANDAMET:** AVANDAMET combines 2 antidiabetic agents with different mechanisms
45 of action to improve glycemic control in patients with type 2 diabetes: Rosiglitazone maleate, a
46 member of the thiazolidinedione class, and metformin hydrochloride, a member of the biguanide
47 class. Thiazolidinediones are insulin sensitizing agents that act primarily by enhancing peripheral
48 glucose utilization, whereas biguanides act primarily by decreasing endogenous hepatic glucose
49 production.

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

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

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

67 **Metformin hydrochloride:** Metformin hydrochloride is an antihyperglycemic agent, which
68 improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial
69 plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral
70 antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal
71 absorption of glucose, and increases peripheral glucose uptake and utilization. Unlike

72 sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes
 73 or normal subjects (except in special circumstances, see PRECAUTIONS) and does not cause
 74 hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting
 75 insulin levels and day-long plasma insulin response may actually decrease.

76 **Pharmacokinetics: Absorption: AVANDAMET:** In a bioequivalence and dose
 77 proportionality study of AVANDAMET 4 mg/500 mg, both the rosiglitazone component and the
 78 metformin component were bioequivalent to coadministered 4 mg rosiglitazone maleate tablet
 79 and 500 mg metformin hydrochloride tablet under fasted conditions (see Table 1). In this study,
 80 dose proportionality of rosiglitazone in the combination formulations of 1 mg/500 mg and
 81 4 mg/500 mg was demonstrated.

82

83 **Table 1. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone and Metformin**

		Pharmacokinetic Parameter			
Regimen	N	AUC _{0-inf} (ng.h/mL)	C _{max} (ng/mL)	T _{max} * (h)	T _{1/2} (h)
Rosiglitazone					
A	25	1,442 (324)	242 (70)	0.95 (0.48-2.47)	4.26 (1.18)
B	25	1,398 (340)	254 (69)	0.57 (0.43-2.58)	3.95 (0.81)
C	24	349 (91)	63.0 (15.0)	0.57 (0.47-1.45)	3.87 (0.88)
Metformin					
A	25	7,116 (2,096)	1,106 (329)	2.97 (1.02-4.02)	3.46 (0.96)
B	25	7,413 (1,838)	1,135 (253)	2.50 (1.03-3.98)	3.36 (0.54)
C	24	6,945 (2,045)	1,080 (327)	2.97 (1.00-5.98)	3.35 (0.59)

84 * Median and range presented for T_{max}

85 Regimen Key: Regimen A = 4 mg/500 mg AVANDAMET

86 Regimen B = 4 mg rosiglitazone maleate tablet + 500 mg metformin
 87 hydrochloride tablet

88 Regimen C = 1 mg/500 mg AVANDAMET

89

90 Administration of AVANDAMET 4 mg/500 mg with food resulted in no change in overall
 91 exposure (AUC) for either rosiglitazone or metformin. However, there were decreases in C_{max} of
 92 both components (22% for rosiglitazone and 15% for metformin, respectively) and a delay in
 93 T_{max} of both components (1.5 hours for rosiglitazone and 0.5 hours for metformin, respectively).
 94 These changes are not likely to be clinically significant. The pharmacokinetics of both the

95 rosiglitazone component and the metformin component of AVANDAMET when taken with food
96 were similar to the pharmacokinetics of rosiglitazone and metformin when administered
97 concomitantly as separate tablets with food.

98 **Absorption: Rosiglitazone maleate:** The absolute bioavailability of rosiglitazone is
99 99%. Peak plasma concentrations are observed about 1 hour after dosing. Maximum plasma
100 concentration (C_{max}) and the area under the curve (AUC) of rosiglitazone increase in a dose-
101 proportional manner over the therapeutic dose range. The elimination half-life is 3 to 4 hours and
102 is independent of dose.

103 **Absorption: Metformin hydrochloride:** The absolute bioavailability of a 500 mg
104 metformin hydrochloride tablet given under fasting conditions is approximately 50% to 60%.
105 Studies using single oral doses of metformin hydrochloride tablets of 500 mg to 1,500 mg, and
106 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses,
107 which is due to decreased absorption rather than an alteration in elimination.

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

112 **Distribution: Metformin hydrochloride:** The apparent volume of distribution (V/F) of
113 metformin following single oral doses of 850 mg metformin hydrochloride averaged
114 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into
115 erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of
116 metformin, steady-state plasma concentrations of metformin are reached within 24 to 48 hours
117 and are generally <1 mcg/mL. During controlled clinical trials, maximum metformin plasma
118 levels did not exceed 5 mcg/mL, even at maximum doses.

119 **Metabolism and Excretion: Rosiglitazone maleate:** Rosiglitazone is extensively
120 metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were
121 N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid.
122 All the circulating metabolites are considerably less potent than parent and, therefore, are not
123 expected to contribute to the insulin-sensitizing activity of rosiglitazone. In vitro data
124 demonstrate that rosiglitazone is predominantly metabolized by cytochrome P450 (CYP)
125 isoenzyme 2C8, with CYP2C9 contributing as a minor pathway. Following oral or intravenous
126 administration of [14 C]rosiglitazone maleate, approximately 64% and 23% of the dose was
127 eliminated in the urine and in the feces, respectively. The plasma half-life of [14 C]related
128 material ranged from 103 to 158 hours.

129 **Metabolism and Excretion: Metformin hydrochloride:** Intravenous single-dose
130 studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and
131 does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary
132 excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance which
133 indicates that tubular secretion is the major route of metformin elimination. Following oral
134 administration, approximately 90% of the absorbed drug is eliminated via the renal route within

135 the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the
136 elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a
137 compartment of distribution.

138 **Special Populations: Renal Impairment:** In subjects with decreased renal function (based
139 on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and
140 the renal clearance is decreased in proportion to the decrease in creatinine clearance (see
141 WARNINGS, also see GLUCOPHAGE[®] prescribing information, and CLINICAL
142 PHARMACOLOGY, Pharmacokinetics). Since metformin is contraindicated in patients with
143 renal impairment, administration of AVANDAMET is contraindicated in these patients.

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

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

152 No pharmacokinetic studies of metformin have been conducted in subjects with hepatic
153 insufficiency.

154 **Geriatric:** Results of the population pharmacokinetics analysis ($n = 716 <65$ years; $n = 331$
155 ≥ 65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone.
156 However, limited data from controlled pharmacokinetic studies of metformin hydrochloride in
157 healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-
158 life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it
159 appears that the change in metformin pharmacokinetics with aging is primarily accounted for by
160 a change in renal function (see GLUCOPHAGE prescribing information and CLINICAL
161 PHARMACOLOGY, Pharmacokinetics). Metformin treatment and therefore treatment with
162 AVANDAMET should not be initiated in patients ≥ 80 years of age unless measurement of
163 creatinine clearance demonstrates that renal function is not reduced (see WARNINGS and
164 DOSAGE AND ADMINISTRATION).

165 **Gender:** Results of the population pharmacokinetics analysis showed that the mean oral
166 clearance of rosiglitazone in female patients ($n = 405$) was approximately 6% lower compared to
167 male patients of the same body weight ($n = 642$). In rosiglitazone and metformin combination
168 studies, efficacy was demonstrated with no gender differences in glycemic response.

169 Metformin pharmacokinetic parameters did not differ significantly between normal subjects
170 and patients with type 2 diabetes when analyzed according to gender (males = 19, females = 16).
171 Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic
172 effect of metformin hydrochloride tablets was comparable in males and females.

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

176 No studies of metformin pharmacokinetic parameters according to race have been performed.
177 In controlled clinical studies of metformin hydrochloride in patients with type 2 diabetes, the
178 antihyperglycemic effect was comparable in whites (n = 249), blacks (n = 51), and Hispanics
179 (n = 24).

180 **Pediatric:** No pharmacokinetic data from studies in pediatric subjects are available for
181 AVANDAMET.

182 Pharmacokinetic parameters of rosiglitazone in pediatric patients were established using a
183 population pharmacokinetic analysis with sparse data from 96 pediatric patients in a single
184 pediatric clinical trial including 33 males and 63 females with ages ranging from 10 to 17 years
185 (weights ranging from 35 to 178.3 kg). Population mean CL/F and V/F of rosiglitazone were
186 3.15 L/hr and 13.5 L, respectively. These estimates of CL/F and V/F were consistent with the
187 typical parameter estimates from a prior adult population analysis.

188 **Drug Interactions**

189 ***Rosiglitazone maleate:***

190 **Drugs that Inhibit, Induce, or are Metabolized by Cytochrome P450:** In vitro drug
191 metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at
192 clinically relevant concentrations. In vitro data demonstrate that rosiglitazone is predominantly
193 metabolized by CYP2C8, and to a lesser extent, 2C9.

194 **Gemfibrozil:** Concomitant administration of gemfibrozil (600 mg twice daily), an inhibitor of
195 CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone AUC by 127%,
196 compared to the administration of rosiglitazone (4 mg once daily) alone. Given the potential for
197 dose-related adverse events with rosiglitazone, a decrease in the dose of rosiglitazone may be
198 needed when gemfibrozil is introduced.

199 **Rifampin:** Rifampin administration (600 mg once a day), an inducer of CYP2C8, for 6 days
200 is reported to decrease rosiglitazone AUC by 66%, compared to the administration of
201 rosiglitazone (8 mg) alone (see PRECAUTIONS).¹

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

205 ***Metformin hydrochloride:***

206 **Furosemide:** A single-dose, metformin-furosemide drug interaction study in healthy subjects
207 demonstrated that pharmacokinetic parameters of both compounds were affected by
208 coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood
209 AUC by 15%, without any significant change in metformin renal clearance. When administered
210 with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than
211 when administered alone, and the terminal half-life was decreased by 32%, without any

212 significant change in furosemide renal clearance. No information is available about the
213 interaction of metformin and furosemide when coadministered chronically.

214 **Nifedipine:** A single-dose, metformin-nifedipine drug interaction study in normal healthy
215 volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max}
216 and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and
217 half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin
218 had minimal effects on nifedipine.

219 **Cationic Drugs:** Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine,
220 quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal
221 tubular secretion theoretically have the potential for interaction with metformin by competing for
222 common renal tubular transport systems. Such interaction between metformin and oral
223 cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose,
224 metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma
225 and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC.
226 There was no change in elimination half-life in the single-dose study. Metformin had no effect
227 on cimetidine pharmacokinetics.

228 **Other:** Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic
229 control. These drugs include thiazides and other diuretics, corticosteroids, phenothiazines,
230 thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics,
231 calcium channel blocking drugs, and isoniazid.

232 In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and
233 ibuprofen were not affected when coadministered in single-dose interaction studies.

234 Metformin is negligibly bound to plasma proteins and is therefore, less likely to interact with
235 highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid.

236 **CLINICAL STUDIES**

237 **Drug-Naïve Patients with Type 2 Diabetes Mellitus**

238 In a 32-week, randomized, double-blind clinical trial, 468 drug-naïve patients with type 2
239 diabetes mellitus inadequately controlled with diet and exercise alone (mean baseline FPG
240 198 mg/dL and mean baseline HbA1c 8.8%) were randomized to AVANDAMET 2 mg/500 mg,
241 rosiglitazone 4 mg, or metformin 500 mg. Doses were increased at 4-week intervals up to a
242 maximum of 8 mg/2,000 mg for AVANDAMET, 8 mg for rosiglitazone, and 2,000 mg for
243 metformin to reach a target mean daily glucose of ≤ 110 mg/dL. Following the initial dosage
244 level, AVANDAMET, rosiglitazone, and metformin were all administered as twice daily
245 regimens. Statistically significant improvements in FPG and HbA1c were observed in patients
246 treated with AVANDAMET compared to either rosiglitazone or metformin alone (see Table 2).
247 However, when considering the choice of therapy for drug-naïve patients, the risk-benefit of
248 initiating monotherapy or dual therapy should be considered.

249

250 **Table 2. Glycemic Parameters in a 32-Week Study of AVANDAMET in Drug-Naïve**
 251 **Patients with Type 2 Diabetes Mellitus**

	AVANDAMET	Rosiglitazone	Metformin
Mean Final Dose	7.2 mg/1,799 mg	7.7 mg	1,847 mg
N	152	155	150
FPG (mg/dL)			
Baseline (mean)	201	194	199
Change from baseline (mean)	-74	-47	-51
Difference between AVANDAMET and monotherapy (adjusted mean)		-22*	-22*
% of patients with ≥ 30 mg/dL decrease from baseline	86%	68%	64%
HbA1c (%)			
Baseline (mean)	8.9%	8.8%	8.8%
Change from baseline (mean)	-2.3%	-1.6%	-1.8%
Difference between AVANDAMET and monotherapy (adjusted mean)		-0.6*	-0.4*
% of patients with HbA1c $\geq 0.7\%$ decrease from baseline	92%	79%	84%
% of Patients with HbA1c $< 7.0\%$	77%	58%	57%

252 * p<0.001 AVANDAMET compared to rosiglitazone or metformin.
 253

254 The lipid profiles of AVANDAMET as well as rosiglitazone and metformin monotherapies
 255 are shown in Table 3.
 256

257 **Table 3. Summary of Mean* Lipid Changes in a 32-Week Study of AVANDAMET in Drug-**
 258 **Naïve Patients with Type 2 Diabetes Mellitus**

	AVANDAMET N [†] = 132	Rosiglitazone N [†] = 128	Metformin N [†] = 117
Total Cholesterol (mg/dL)			
Baseline (mean)	200.4	198.4	201.6
% Change from baseline (mean)	-2.2%	5.3%	-9.0%
LDL (mg/dL)			
Baseline (mean)	113.8	114.6	116.0
% Change from baseline (mean)	-0.2%	4.5%	-10.7%
HDL (mg/dL)			
Baseline (mean)	42.6	42.8	42.9
% Change from baseline (mean)	5.8%	3.1%	0.0%
Triglycerides (mg/dL)			
Baseline (mean)	180.3	166.6	175.7
% Change from baseline (mean)	-18.7%	-4.8%	-15.4%

259 * Data presented as geometric means throughout table.

260 † N = number of subjects with a baseline and end of treatment value.

261
 262 Patients screened in the double-blind clinical trial described above with HbA1c >11% or FPG
 263 >270 mg/dL were not eligible for blinded treatment but were treated with open-label
 264 AVANDAMET (4 mg/1,000 mg up to a maximum dose of 8 mg/2,000 mg). Treatment with
 265 AVANDAMET reduced mean HbA1c from a baseline of 11.8% to 7.8% and mean FPG from a
 266 baseline of 305 mg/dL to 166 mg/dL. Given the lack of direct comparators in this evaluation,
 267 determination of the exact contribution of rosiglitazone and metformin as well as diet and
 268 exercise, to the observed improvement in glycemic control is not possible.

269 **AVANDAMET Therapy in Patients with Type 2 Diabetes Mellitus Treated with**
 270 **Metformin Hydrochloride**

271 AVANDAMET was not studied in patients previously treated with metformin monotherapy;
 272 however, the combination of rosiglitazone maleate and metformin hydrochloride was compared
 273 to rosiglitazone and metformin monotherapies in clinical trials. Bioequivalence between
 274 AVANDAMET and coadministered rosiglitazone maleate tablets and metformin hydrochloride
 275 tablets has been demonstrated (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

276 The pattern of LDL, HDL, and total cholesterol changes following therapy with rosiglitazone
 277 in combination with metformin was generally similar to those seen with rosiglitazone
 278 monotherapy, and a small decrease in mean triglycerides was observed with the combination
 279 therapy.

280 A total of 670 patients with type 2 diabetes participated in two 26-week, randomized, double-
 281 blind, placebo/active-controlled studies designed to assess the efficacy of rosiglitazone in
 282 combination with metformin. Rosiglitazone maleate, administered in either once-daily or

283 twice-daily dosing regimens, was added to the therapy of patients who were inadequately
 284 controlled on 2.5 grams/day of metformin hydrochloride.

285 In one study, patients inadequately controlled on 2.5 grams/day of metformin hydrochloride
 286 (mean baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were randomized to receive
 287 rosiglitazone 4 mg once daily, rosiglitazone 8 mg once daily, or placebo in addition to
 288 metformin. A statistically significant improvement in FPG and HbA1c was observed in patients
 289 treated with the combinations of metformin and rosiglitazone 4 mg once daily and rosiglitazone
 290 8 mg once daily, versus patients continued on metformin alone (see Table 4).
 291

292 **Table 4. Glycemic Parameters in a 26-Week Study of Rosiglitazone Added to Metformin**
 293 **Therapy**

	Metformin	Rosiglitazone 4 mg once daily + metformin	Rosiglitazone 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 metformin alone (adjusted mean)		-40*	-53*
% of patients with ≥ 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 metformin alone (adjusted mean)		-1.0*	-1.2*
% of patients with HbA1c $\geq 0.7\%$ decrease from baseline	11%	45%	52%

294 * p<0.0001 compared to metformin.
 295

296 In a second 26-week study, patients with type 2 diabetes inadequately controlled on
 297 2.5 grams/day of metformin hydrochloride who were randomized to receive the combination of
 298 rosiglitazone 4 mg twice daily and metformin (N = 105) showed a statistically significant
 299 improvement in glycemic control with a mean treatment effect for FPG of -56 mg/dL and a
 300 mean treatment effect for HbA1c of -0.8% over metformin alone. The combination of metformin
 301 and rosiglitazone resulted in lower levels of FPG and HbA1c than either agent alone.

302 **AVANDAMET Combination with Insulin:** After an 8-week single-blind AVANDAMET
 303 run-in (rosiglitazone 8 mg/metformin 2,000 mg daily), 324 patients with type 2 diabetes mellitus
 304 with fasting plasma glucose (FPG) ≥ 126 mg/dL were randomized to receive AVANDAMET

305 8 mg/2,000 mg plus insulin (insulin add-on therapy) or placebo plus insulin (switch to insulin
 306 monotherapy) in a 24-week, double-blind, multicenter study. Most of the patients had been
 307 treated with metformin therapy (~20% monotherapy and ~70% combination therapy with a
 308 sulfonylurea) before entering the AVANDAMET run-in. Patients with congestive heart failure or
 309 who developed edema or whose edema worsened on AVANDAMET therapy during the run-in
 310 were not eligible for randomization. Premixed insulin was initiated at 12 units administered
 311 twice daily and could be adjusted at a minimum of every 3 to 5 days to achieve target capillary
 312 blood glucose values (pre-breakfast and pre-evening meals FPG \leq 117.0 mg/dL).

313

314 **Table 5. Glycemic Parameters in a 24-Week AVANDAMET + Insulin Combination Study**

	AVANDAMET + Insulin	Insulin Monotherapy
N	161	157
FPG (mg/dL)		
Baseline (mean)	196	195
Mean change from baseline	-61	-34
Difference from insulin monotherapy	-26*	
% of patients with \geq 30 mg/dL decrease from baseline	71%	48%
HbA1c (%)		
Baseline (mean)	8.7	8.8
Mean change from baseline	-2.0	-1.3
% of patients with HbA1c \geq 0.7% decrease from baseline	84%	72%
Difference from insulin monotherapy	-0.7*	
% of patients with HbA1c <7%	70%	34%

315 * Adjusted mean, $p < 0.0001$ compared to insulin monotherapy.

316

317 Patients who had insulin added to maximal AVANDAMET therapy had significantly greater
 318 reductions in FPG and HbA1c compared to patients who were switched to insulin monotherapy
 319 (see Table 5). At Week 24, the mean final total daily insulin dose was significantly lower in the
 320 AVANDAMET plus insulin group compared to the insulin monotherapy group (33 U versus
 321 59 U; mean adjusted treatment difference of 25 U, $p < 0.0001$).

322 **INDICATIONS AND USAGE**

323 AVANDAMET is indicated as an adjunct to diet and exercise to improve glycemic control in
 324 patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and metformin
 325 therapy is appropriate.

326 Management of type 2 diabetes mellitus should include diet control. Caloric restriction,
 327 weight loss, and exercise are essential for the proper treatment of the diabetic patient because
 328 they help improve insulin sensitivity. This is important not only in the primary treatment of type

329 2 diabetes but also in maintaining the efficacy of drug therapy. Prior to initiation or escalation of
330 oral antidiabetic therapy in patients with type 2 diabetes mellitus, secondary causes of poor
331 glycemic control, e.g., infection, should be investigated and treated.

332 **CONTRAINDICATIONS**

333 AVANDAMET tablets are contraindicated in patients with:

- 334 1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL
335 [males], ≥ 1.4 mg/dL [females], or abnormal creatinine clearance), which may also result
336 from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and
337 septicemia (see WARNINGS and PRECAUTIONS).
- 338 2. Known hypersensitivity to rosiglitazone maleate or metformin hydrochloride.
- 339 3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
340 Diabetic ketoacidosis should be treated with insulin.

341 AVANDAMET should be temporarily discontinued in patients undergoing radiologic studies
342 involving intravascular administration of iodinated contrast materials, because use of such
343 products may result in acute alteration of renal function (see also PRECAUTIONS).

344 **WARNINGS**

345 **Metformin hydrochloride**

346 **Lactic Acidosis**

347 **Lactic acidosis is a rare, but serious, metabolic complication that can occur due to**
348 **metformin accumulation during treatment with AVANDAMET; when it occurs, it is fatal**
349 **in approximately 50% of cases. Lactic acidosis may also occur in association with a number**
350 **of pathophysiologic conditions, including diabetes mellitus, and whenever there is**
351 **significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by**
352 **elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances**
353 **with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is**
354 **implicated as the cause of lactic acidosis, metformin plasma levels >5 mcg/mL are generally**
355 **found.**

356 **The reported incidence of lactic acidosis in patients receiving metformin hydrochloride**
357 **is very low (approximately 0.03 cases/1,000 patient years of exposure, with approximately**
358 **0.015 fatal cases/1,000 patient years of exposure). Reported cases have occurred primarily**
359 **in diabetic patients with significant renal insufficiency, including both intrinsic renal**
360 **disease and renal hypoperfusion, often in the setting of multiple concomitant**
361 **medical/surgical problems and multiple concomitant medications. Patients with congestive**
362 **heart failure requiring pharmacologic management, in particular those with unstable or**
363 **acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at**
364 **increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal**
365 **dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly**
366 **decreased by regular monitoring of renal function in patients taking AVANDAMET and**

367 by use of the minimum effective dose of AVANDAMET. In particular, treatment of the
368 elderly should be accompanied by careful monitoring of renal function. Treatment with
369 AVANDAMET should not be initiated in patients ≥ 80 years of age unless measurement of
370 creatinine clearance demonstrates that renal function is not reduced, as these patients are
371 more susceptible to developing lactic acidosis. In addition, AVANDAMET should be
372 promptly withheld in the presence of any condition associated with hypoxemia,
373 dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability
374 to clear lactate, AVANDAMET should generally be avoided in patients with clinical or
375 laboratory evidence of hepatic disease. Patients should be cautioned against excessive
376 alcohol intake, either acute or chronic, when taking AVANDAMET, since alcohol
377 potentiates the effects of metformin hydrochloride on lactate metabolism. In addition,
378 AVANDAMET should be temporarily discontinued prior to any intravascular
379 radiocontrast study and for any surgical procedure (see also PRECAUTIONS).

380 The onset of lactic acidosis often is subtle, and accompanied only by nonspecific
381 symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and
382 nonspecific abdominal distress. There may be associated hypothermia, hypotension, and
383 resistant bradyarrhythmias with more marked acidosis. The patient and the patient's
384 physician must be aware of the possible importance of such symptoms and the patient
385 should be instructed to notify the physician immediately if they occur (see also
386 PRECAUTIONS). AVANDAMET should be withdrawn until the situation is clarified.
387 Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels, and
388 even blood metformin levels may be useful. Once a patient is stabilized on any dose level of
389 AVANDAMET, gastrointestinal symptoms, which are common during initiation of
390 therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms
391 could be due to lactic acidosis or other serious disease.

392 Levels of fasting venous plasma lactate above the upper limit of normal but less than
393 5 mmol/L in patients taking AVANDAMET do not necessarily indicate impending lactic
394 acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes
395 or obesity, vigorous physical activity or technical problems in sample handling (see also
396 PRECAUTIONS).

397 Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis
398 lacking evidence of ketoacidosis (ketonuria and ketonemia).

399 Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a
400 patient with lactic acidosis who is taking AVANDAMET, the drug should be discontinued
401 immediately and general supportive measures promptly instituted. Because metformin
402 hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good
403 hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis
404 and remove the accumulated metformin. Such management often results in prompt
405 reversal of symptoms and recovery (see also CONTRAINDICATIONS and
406 PRECAUTIONS).

407

408 **Rosiglitazone maleate**

409 **Cardiac Failure and Other Cardiac Effects:** Rosiglitazone, like other thiazolidinediones,
 410 alone or in combination with other antidiabetic agents, can cause fluid retention, which may
 411 exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart
 412 failure. AVANDAMET should be discontinued if any deterioration in cardiac status occurs.

413 Patients with congestive heart failure (CHF) New York Heart Association (NYHA) Class 1
 414 and 2 treated with rosiglitazone have an increased risk of cardiovascular events. A 52-week,
 415 double-blind, placebo-controlled echocardiographic study was conducted in 224 patients with
 416 type 2 diabetes mellitus and NYHA Class 1 or 2 CHF (ejection fraction $\leq 45\%$) on background
 417 antidiabetic and CHF therapy. An independent committee conducted a blinded evaluation of
 418 fluid-related events (including congestive heart failure) and cardiovascular hospitalizations
 419 according to predefined criteria (adjudication). Separate from the adjudication, other
 420 cardiovascular adverse events were reported by investigators. Although no treatment difference
 421 in change from baseline of ejection fractions was observed, more cardiovascular adverse events
 422 were observed with rosiglitazone treatment compared to placebo during the 52-week study. (See
 423 Table 6.)

424

425 **Table 6. Emergent Cardiovascular Adverse Events in Patients with Congestive Heart**
 426 **Failure (NYHA Class 1 and 2) Treated with Rosiglitazone or Placebo (in Addition to**
 427 **Background Antidiabetic and CHF Therapy)**

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

428 * Includes hospitalization for any cardiovascular reason.

429

430 Patients with NYHA Class 3 and 4 cardiac status were not studied during the clinical trials.
431 AVANDAMET is not recommended in patients with NYHA Class 3 and 4 cardiac status.

432 In combination with insulin, thiazolidinediones may increase the risk of other cardiovascular
433 adverse events. In three 26-week trials in patients with type 2 diabetes, 216 received 4 mg of
434 rosiglitazone plus insulin, 322 received 8 mg of rosiglitazone plus insulin, and 338 received
435 insulin alone. These trials included patients with long-standing diabetes and a high prevalence of
436 pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart
437 disease, vascular disease, and congestive heart failure. In these clinical studies, an increased
438 incidence of edema, cardiac failure, and other cardiovascular adverse events was seen in patients
439 on rosiglitazone and insulin combination therapy compared to insulin and placebo. Patients who
440 experienced cardiovascular events were on average older and had a longer duration of diabetes.
441 These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of rosiglitazone.
442 In this population, however, it was not possible to determine specific risk factors that could be
443 used to identify all patients at risk of heart failure and other cardiovascular events on
444 combination therapy. Three of 10 patients who developed cardiac failure on combination therapy
445 during the double-blind part of the fixed-dose studies had no known prior evidence of congestive
446 heart failure, or pre-existing cardiac condition.

447 In a double-blind study in type 2 diabetes patients with chronic renal failure (112 received
448 4 mg or 8 mg of rosiglitazone plus insulin and 108 received insulin alone), there was no
449 difference in cardiovascular adverse events with rosiglitazone in combination with insulin
450 compared to insulin alone.

451 Patients treated with combination AVANDAMET and insulin should be monitored for
452 cardiovascular adverse events. The combination therapy should be discontinued in patients who
453 do not respond as manifested by a reduction in HbA1c or insulin dose after 4 to 5 months of
454 therapy or who develop any significant adverse events. (See ADVERSE REACTIONS.)

455 **PRECAUTIONS**

456 ***Metformin hydrochloride:***

457 **Monitoring of renal function:** Metformin is known to be substantially excreted by the
458 kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of
459 impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of
460 normal for their age should not receive AVANDAMET. In patients with advanced age,
461 AVANDAMET should be carefully titrated to establish the minimum dose for adequate
462 glycemic effect, because aging is associated with reduced renal function. In elderly patients,
463 particularly those ≥ 80 years of age, renal function should be monitored regularly and, generally,
464 AVANDAMET should not be titrated to the maximum dose of the metformin component, i.e.,
465 2,000 mg (see WARNINGS and DOSAGE AND ADMINISTRATION).

466 Before initiation of therapy with AVANDAMET and at least annually thereafter, renal
467 function should be assessed and verified as normal. In patients in whom development of renal

468 dysfunction is anticipated, renal function should be assessed more frequently and
469 AVANDAMET discontinued if evidence of renal impairment is present.

470 **Use of concomitant medications that may affect renal function or metformin**
471 **disposition:** Concomitant medication(s) that may affect renal function or result in significant
472 hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs
473 that are eliminated by renal tubular secretion (see PRECAUTIONS, Drug Interactions), should
474 be used with caution.

475 **Radiologic studies involving the use of intravascular iodinated contrast materials**
476 **(for example, intravenous urogram, intravenous cholangiography, angiography,**
477 **and computed tomography [CT] scans with contrast materials):** Intravascular contrast
478 studies with iodinated materials can lead to acute alteration of renal function and have been
479 associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS).
480 Therefore, in patients in whom any such study is planned, AVANDAMET should be temporarily
481 discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the
482 procedure and reinstated only after renal function has been re-evaluated and found to be
483 normal.

484 **Hypoxic states:** Cardiovascular collapse (shock) from whatever cause, acute congestive heart
485 failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been
486 associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in
487 patients receiving AVANDAMET, the drug should be promptly discontinued.

488 **Surgical procedures:** Use of AVANDAMET should be temporarily suspended for any
489 surgical procedure (except minor procedures not associated with restricted intake of food and
490 fluids) and should not be restarted until the patient's oral intake has resumed and renal function
491 has been evaluated as normal.

492 **Alcohol intake:** Alcohol is known to potentiate the effect of metformin on lactate metabolism.
493 Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while
494 receiving AVANDAMET.

495 **Impaired hepatic function:** Since impaired hepatic function has been associated with some
496 cases of lactic acidosis, AVANDAMET should generally be avoided in patients with clinical or
497 laboratory evidence of hepatic disease.

498 **Vitamin B₁₂ levels:** In controlled clinical trials of metformin hydrochloride of 29 weeks'
499 duration, a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, without
500 clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly
501 due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very
502 rarely associated with anemia and appears to be rapidly reversible with discontinuation of
503 metformin or vitamin B₁₂ supplementation. Measurement of hematologic parameters on an
504 annual basis is advised in patients on AVANDAMET and any apparent abnormalities should be
505 appropriately investigated and managed (see PRECAUTIONS, Laboratory Tests). Certain
506 individuals (those with inadequate vitamin B₁₂ or calcium intake or absorption) appear to be

507 predisposed to developing subnormal vitamin B₁₂ levels. In these patients, routine serum vitamin
508 B₁₂ measurements at 2- to 3-year intervals may be useful.

509 **Change in clinical status of previously controlled diabetic:** A patient with type 2
510 diabetes previously well-controlled on AVANDAMET who develops laboratory abnormalities or
511 clinical illness (especially vague and poorly defined illness) should be evaluated promptly for
512 evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and
513 ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If
514 acidosis of either form occurs, AVANDAMET must be stopped immediately and other
515 appropriate corrective measures initiated (see also WARNINGS).

516 **Hypoglycemia:** Hypoglycemia does not occur in patients receiving metformin hydrochloride
517 alone under usual circumstances of use but could occur when caloric intake is deficient, when
518 strenuous exercise is not compensated by caloric supplementation, or during concomitant use
519 with hypoglycemic agents (such as sulfonylureas or insulin) or ethanol. Elderly, debilitated or
520 malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication
521 are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize
522 in the elderly and in people who are taking β -adrenergic blocking drugs.

523 **Loss of control of blood glucose:** When a patient stabilized on any diabetic regimen is
524 exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic
525 control may occur. At such times, it may be necessary to withhold AVANDAMET and
526 temporarily administer insulin. AVANDAMET may be reinstated after the acute episode is
527 resolved.

528 ***Rosiglitazone maleate:***

529 **General:** Due to its mechanism of action, rosiglitazone is active only in the presence of
530 endogenous insulin. Therefore, AVANDAMET should not be used in patients with type 1
531 diabetes.

532 **Hypoglycemia:** Patients receiving rosiglitazone in combination with other hypoglycemic
533 agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent
534 may be necessary.

535 **Edema:** AVANDAMET should be used with caution in patients with edema. In a clinical study
536 in healthy volunteers who received rosiglitazone 8 mg once daily for 8 weeks, there was a
537 statistically significant increase in median plasma volume compared to placebo. Since
538 thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or
539 lead to congestive heart failure, AVANDAMET should be used with caution in patients at risk
540 for heart failure. Patients should be monitored for signs and symptoms of heart failure (see
541 WARNINGS, Rosiglitazone maleate, Cardiac Failure and Other Cardiac Effects and
542 PRECAUTIONS, Information for Patients).

543 In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was
544 reported in patients treated with rosiglitazone maleate, and may be dose related. Patients with
545 ongoing edema are more likely to have adverse events associated with edema if started on
546 combination therapy with insulin and rosiglitazone (see ADVERSE REACTIONS).

547 **Macular Edema:** Macular edema has been reported in postmarketing experience in some
548 diabetic patients who were taking rosiglitazone or another thiazolidinedione. Some patients
549 presented with blurred vision or decreased visual acuity, but some patients appear to have been
550 diagnosed on routine ophthalmologic examination. Most patients had peripheral edema at the
551 time macular edema was diagnosed. Some patients had improvement in their macular edema
552 after discontinuation of their thiazolidinedione. Patients with diabetes should have regular eye
553 exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association.
554 Additionally, any diabetic who reports any kind of visual symptom should be promptly referred
555 to an ophthalmologist, regardless of the patient's underlying medications or other physical
556 findings. (See ADVERSE REACTIONS, Postmarketing Experience.)

557 **Weight Gain:** Dose-related weight gain was seen with rosiglitazone alone and rosiglitazone
558 together with other hypoglycemic agents (see Table 7). No overall change in median weight was
559 observed with AVANDAMET in drug-naïve patients. The mechanism of weight gain with
560 rosiglitazone is unclear but probably involves a combination of fluid retention and fat
561 accumulation.

562

563 **Table 7. Weight Changes (kg) From Baseline at Endpoint During Clinical Trials**
[Median (25th, 75th, Percentile)]

Monotherapy				
Duration	Control Group		Rosiglitazone 4 mg	Rosiglitazone 8 mg
26 weeks	Placebo	-0.9 (-2.8, 0.9) n = 210	1.0 (0.9, 3.6) n = 436	3.1 (1.1, 5.8) n = 439
52 weeks	Sulfonylurea	2.0 (0, 4.0) n = 173	2.0 (-0.6, 4.0) n = 150	2.6 (0, 5.3) n = 157
Combination Therapy				
			Rosiglitazone plus Control Therapy	
Duration	Control Group		Rosiglitazone 4 mg	Rosiglitazone 8 mg
24-26 weeks	Sulfonylurea	0 (-1.0, 1.3) n = 1,155	2.2 (0.5, 4.0) n = 613	3.5 (1.4, 5.9) n = 841
26 weeks	Metformin	-1.4 (-3.2, 0.2) n = 175	0.8 (-1.0, 2.6) n = 100	2.1 (0, 4.3) n = 184
26 weeks	Insulin	0.9 (-0.5, 2.7) n = 162	4.1 (1.4, 6.3) n = 164	5.4 (3.4, 7.3) n = 150
AVANDAMET in Drug Naïve Patients				
Duration	Control Groups		AVANDAMET	
32 weeks	Metformin	-2.2 (-5.5, -0.5) n = 123	0.05 kg (-3.45, 3.0) n = 136	
	Rosiglitazone	1.7 (-1.2, 4.5) n = 136		
AVANDAMET plus Insulin				
Duration	Control Group		AVANDAMET plus INSULIN	
24 weeks	Insulin	2.6 kg (0.3, 4.8) n = 145	3.3 kg (1.5, 6.0) n = 147	

564
565 In postmarketing experience with rosiglitazone alone or in combination with other
566 hypoglycemic agents, there have been rare reports of unusually rapid increases in weight and
567 increases in excess of that generally observed in clinical trials. Patients who experience such
568 increases should be assessed for fluid accumulation and volume-related events such as excessive
569 edema and congestive heart failure.

570 **Hematologic:** Across all controlled clinical studies in adults, decreases in hemoglobin and
571 hematocrit (mean decreases in individual studies of approximately ≤ 1.0 gram/dL and $\leq 3.3\%$,
572 respectively) were observed for rosiglitazone maleate alone and in combination with other
573 hypoglycemic agents. The changes occurred primarily during the first 3 months following
574 initiation of rosiglitazone therapy or following an increase in rosiglitazone dose. The decrease in
575 hemoglobin was seen more frequently in combination rosiglitazone and metformin therapy than

576 in rosiglitazone therapy alone. Vitamin B₁₂ deficiency may contribute to the observed reductions
577 in hemoglobin (see PRECAUTIONS, Metformin hydrochloride, Vitamin B₁₂ levels). White
578 blood cell counts also decreased slightly in adult patients treated with rosiglitazone. Small
579 decreases in hemoglobin and hematocrit have also been reported in pediatric patients treated with
580 rosiglitazone. The observed changes may be related to the increased plasma volume observed
581 with treatment with rosiglitazone and may be dose related (see ADVERSE REACTIONS,
582 Laboratory Abnormalities).

583 **Ovulation:** Therapy with rosiglitazone, like other thiazolidinediones, may result in ovulation in
584 some premenopausal anovulatory women. As a result, these patients may be at an increased risk
585 for pregnancy while taking AVANDAMET (see PRECAUTIONS, Pregnancy, Pregnancy
586 Category C). Thus, adequate contraception in premenopausal women should be recommended.
587 This possible effect has not been specifically investigated in clinical studies so the frequency of
588 this occurrence is not known.

589 Although hormonal imbalance has been seen in preclinical studies (see PRECAUTIONS,
590 Carcinogenesis, Mutagenesis, Impairment of Fertility), the clinical significance of this finding is
591 not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with
592 AVANDAMET should be reviewed.

593 **Hepatic Effects:** Another drug of the thiazolidinedione class, troglitazone, was associated with
594 idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death were
595 reported during clinical use. In pre-approval controlled clinical trials in patients with type 2
596 diabetes, troglitazone was more frequently associated with clinically significant elevations in
597 liver enzymes (ALT >3X upper limit of normal) compared to placebo. Very rare cases of
598 reversible jaundice were also reported.

599 In pre-approval clinical studies in 4,598 patients treated with rosiglitazone maleate,
600 encompassing approximately 3,600 patient years of exposure, there was no signal of
601 drug-induced hepatotoxicity or elevation of ALT levels. In the pre-approval controlled trials,
602 0.2% of patients treated with rosiglitazone had elevations in ALT >3X the upper limit of normal
603 compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients
604 treated with rosiglitazone were reversible and were not clearly causally related to therapy with
605 rosiglitazone.

606 In postmarketing experience with rosiglitazone maleate, reports of hepatitis and of hepatic
607 enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely,
608 these reports have involved hepatic failure with and without fatal outcome, although causality
609 has not been established. Rosiglitazone is structurally related to troglitazone, a thiazolidinedione
610 no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity
611 and rare cases of liver failure, liver transplants, and death during clinical use. Pending the
612 availability of the results of additional large, long-term controlled clinical trials and additional
613 postmarketing safety data, it is recommended that patients treated with AVANDAMET undergo
614 periodic monitoring of liver enzymes.

615 Liver enzymes should be checked prior to the initiation of therapy with AVANDAMET in all
616 patients and periodically thereafter per the clinical judgement of the healthcare professional.
617 Therapy with AVANDAMET should not be initiated in patients with increased baseline liver
618 enzyme levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes
619 (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with AVANDAMET
620 should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or
621 continuation of, therapy with AVANDAMET in patients with mild liver enzyme elevations
622 should proceed with caution and include close clinical follow-up, including more frequent liver
623 enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time
624 ALT levels increase to >3X the upper limit of normal in patients on therapy with
625 AVANDAMET, liver enzyme levels should be rechecked as soon as possible. If ALT levels
626 remain >3X the upper limit of normal, therapy with AVANDAMET should be discontinued.

627 If any patient develops symptoms suggesting hepatic dysfunction, which may include
628 unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, and/or dark urine, liver
629 enzymes should be checked. If jaundice is observed, drug therapy should be discontinued.

630 In addition, if the presence of hepatic disease or hepatic dysfunction of sufficient magnitude to
631 predispose to lactic acidosis is confirmed, therapy with AVANDAMET should be discontinued.

632 There are no data available from clinical trials to evaluate the safety of AVANDAMET in
633 patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on
634 troglitazone. AVANDAMET should not be used in patients who experienced jaundice while
635 taking troglitazone.

636 **Laboratory Tests:** Periodic fasting blood glucose and HbA1c measurements should be
637 performed to monitor therapeutic response.

638 Liver enzyme monitoring is recommended prior to initiation of therapy with AVANDAMET
639 in all patients and periodically thereafter (see PRECAUTIONS, Hepatic Effects and ADVERSE
640 REACTIONS, Laboratory Abnormalities, *Serum Transaminase Levels*).

641 Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and
642 red blood cell indices) and renal function (serum creatinine) should be performed, at least on an
643 annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is
644 suspected, vitamin B₁₂ deficiency should be excluded.

645 **Information for Patients:** Patients should be informed of the potential risks and advantages of
646 AVANDAMET and of alternative modes of therapy. They should also be informed about the
647 importance of adherence to dietary instructions, weight loss, and a regular exercise program
648 because these methods help improve insulin sensitivity. The importance of regular testing of
649 blood glucose, glycosylated hemoglobin (HbA1c), renal function, and hematologic parameters
650 should be emphasized. Patients should be advised that AVANDAMET can begin to take effect 1
651 to 2 weeks after initiation, however it can take 2 to 3 months to see the full effect of glycemic
652 improvement.

653 The risks of lactic acidosis, its symptoms, and conditions that predispose to its development,
654 as noted in the WARNINGS and PRECAUTIONS sections, should be explained to patients.

655 Patients should be advised to discontinue AVANDAMET immediately and to promptly notify
656 their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence,
657 or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of
658 AVANDAMET, gastrointestinal symptoms, which are common during initiation of metformin
659 therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be
660 due to lactic acidosis or other serious disease.

661 Patients should be counseled against excessive alcohol intake, either acute or chronic, while
662 receiving AVANDAMET.

663 Patients should be informed that blood will be drawn to check their liver function prior to the
664 start of therapy and periodically thereafter per the clinical judgement of the healthcare
665 professional. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue,
666 anorexia, or dark urine should immediately report these symptoms to their physician.

667 Patients who experience an unusually rapid increase in weight or edema or who develop
668 shortness of breath or other symptoms of heart failure while on AVANDAMET should
669 immediately report these symptoms to their physician.

670 Therapy with AVANDAMET, like other thiazolidinediones, may result in ovulation in some
671 premenopausal anovulatory women. As a result, these patients may be at an increased risk for
672 pregnancy while taking AVANDAMET (see PRECAUTIONS, Pregnancy, Pregnancy
673 Category C). Thus, adequate contraception in premenopausal women should be recommended.
674 This possible effect has not been specifically investigated in clinical studies so the frequency of
675 this occurrence is not known.

676 **Drug Interactions:** An inhibitor of CYP2C8 (such as gemfibrozil) may increase the AUC of
677 rosiglitazone and an inducer of CYP2C8 (such as rifampin) may decrease the AUC of
678 rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during
679 treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical
680 response.

681 Although drug interactions with cationic drugs (e.g., amiloride, digoxin, morphine,
682 procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) remain
683 theoretical (except for cimetidine), careful patient monitoring and dose adjustment of
684 AVANDAMET and/or the interfering drug is recommended in patients who are taking cationic
685 medications that are excreted via the proximal renal tubular secretory system.

686 When drugs that produce hyperglycemia which may lead to loss of glycemic control are
687 administered to a patient receiving AVANDAMET, the patient should be closely observed to
688 maintain adequate glycemic control. (See CLINICAL PHARMACOLOGY, Drug Interactions.)

689 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No animal studies have been
690 conducted with the combined products in AVANDAMET. The following data are based on
691 findings in studies performed with rosiglitazone or metformin individually.

692 **Rosiglitazone maleate:** A 2-year carcinogenicity study was conducted in Charles River
693 CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to
694 approximately 12 times human AUC at the maximum recommended human daily dose of the

695 rosiglitazone component of AVANDAMET). Sprague-Dawley rats were dosed for 2 years by
696 oral gavage at doses of 0.05, 0.3, and 2 mg/kg/day (highest dose equivalent to approximately 10
697 and 20 times human AUC at the maximum recommended human daily dose of the rosiglitazone
698 component of AVANDAMET for male and female rats, respectively).

699 Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of
700 adipose hyperplasia in the mouse at doses ≥ 1.5 mg/kg/day (approximately 2 times human AUC
701 at the maximum recommended human daily dose of the rosiglitazone component of
702 AVANDAMET). In rats, there was a significant increase in the incidence of benign adipose
703 tissue tumors (lipomas) at doses ≥ 0.3 mg/kg/day (approximately 2 times human AUC at the
704 maximum recommended human daily dose of the rosiglitazone component of AVANDAMET).
705 These proliferative changes in both species are considered due to the persistent pharmacological
706 overstimulation of adipose tissue.

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

712 Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day
713 (approximately 116 times human AUC at the maximum recommended human daily dose of the
714 rosiglitazone component of AVANDAMET). Rosiglitazone altered estrous cyclicity
715 (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower
716 plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the
717 maximum recommended human daily dose of the rosiglitazone component of AVANDAMET,
718 respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC
719 at the maximum recommended human daily dose of the rosiglitazone component of
720 AVANDAMET). In juvenile rats dosed from 27 days of age through to sexual maturity (at up to
721 40 mg/kg/day), there was no effect on male reproductive performance, or on estrous cyclicity,
722 mating performance or pregnancy incidence in females (approximately 68 times human AUC at
723 the maximum recommended daily dose of rosiglitazone). In monkeys, rosiglitazone (0.6 and
724 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended
725 human daily dose of the rosiglitazone component of AVANDAMET, respectively) diminished
726 the follicular phase rise in serum estradiol with consequential reduction in the luteinizing
727 hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for
728 these effects appears to be direct inhibition of ovarian steroidogenesis.

729 **Metformin hydrochloride:** Long-term carcinogenicity studies have been performed in rats
730 (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and
731 including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately
732 4 times the maximum recommended human daily dose of 2,000 mg of the metformin component
733 of AVANDAMET based on body surface area comparisons. No evidence of carcinogenicity with
734 metformin was found in either male or female mice. Similarly, there was no tumorigenic

735 potential observed with metformin in male rats. There was, however, an increased incidence of
736 benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

737 There was no evidence of mutagenic potential of metformin in the following in vitro tests:
738 Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal
739 aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also
740 negative.

741 Fertility of male or female rats was unaffected by metformin when administered at doses as
742 high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human
743 daily dose of the metformin component of AVANDAMET based on body surface area
744 comparisons.

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

751 **Pregnancy:** Pregnancy Category C. All pregnancies have a background risk of birth defects,
752 loss, or other adverse outcome regardless of drug exposure. This background risk is increased in
753 pregnancies complicated by hyperglycemia and may be decreased with good metabolic control.
754 It is essential for patients with diabetes or history of gestational diabetes to maintain good
755 metabolic control before conception and throughout pregnancy. Careful monitoring of glucose
756 control is essential in such patients. Most experts recommend that insulin monotherapy be used
757 during pregnancy to maintain blood glucose levels as close to normal as possible.
758 AVANDAMET should not be used during pregnancy.

759 **Human Data:** There are no adequate and well-controlled studies in pregnant women with
760 AVANDAMET or its individual components.

761 **Rosiglitazone maleate:** Rosiglitazone has been reported to cross the human placenta and be
762 detectable in fetal tissue. The clinical significance of these findings is unknown.

763 **Animal Studies:** No animal studies have been conducted with the combined products in
764 AVANDAMET. The following data are based on findings in studies performed with
765 rosiglitazone or metformin individually.

766 **Rosiglitazone maleate:** There was no effect on implantation or the embryo with rosiglitazone
767 treatment during early pregnancy in rats, but treatment during mid-late gestation was associated
768 with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed
769 at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human
770 AUC at the maximum recommended human daily dose of the rosiglitazone component of
771 AVANDAMET, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day).
772 Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and
773 postnatal growth, with growth retardation reversible after puberty. For effects on the placenta,
774 embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in

775 rabbits. These no-effect levels are approximately 4 times human AUC at the maximum
776 recommended human daily dose of the rosiglitazone component of AVANDAMET.
777 Rosiglitazone reduced the number of uterine implantations and live offspring when juvenile
778 female rats were treated at 40 mg/kg/day from 27 days of age through to sexual maturity
779 (approximately 68 times human AUC at the maximum recommended daily dose). The no-effect
780 level was 2 mg/kg/day (approximately 4 times human AUC at the maximum recommended daily
781 dose). There was no effect on pre- or post-natal survival or growth.

782 **Metformin hydrochloride:** Metformin was not teratogenic in rats and rabbits at doses up to
783 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended
784 human daily dose of 2,000 mg based on body surface area comparisons for rats and rabbits,
785 respectively. Determination of fetal concentrations demonstrated a partial placental barrier to
786 metformin.

787 **Labor and Delivery:** The effect of AVANDAMET or its components on labor and delivery in
788 humans is unknown.

789 **Nursing Mothers:** No studies have been conducted with the combined components of
790 AVANDAMET. In studies performed with the individual components, both rosiglitazone-related
791 material and metformin were detectable in milk from lactating rats. It is not known whether
792 rosiglitazone and/or metformin is excreted in human milk. Because many drugs are excreted in
793 human milk, AVANDAMET should not be administered to a nursing woman. If AVANDAMET
794 is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy
795 should be considered.

796 **Pediatric Use:** Safety and effectiveness of AVANDAMET in pediatric patients have not been
797 established. AVANDAMET and rosiglitazone are not indicated for use in pediatric patients.

798 **Geriatric Use:** Metformin is known to be substantially excreted by the kidney and because the
799 risk of serious adverse reactions to the drug is greater in patients with impaired renal function,
800 AVANDAMET should only be used in patients with normal renal function (see
801 CONTRAINDICATIONS, WARNINGS, and CLINICAL PHARMACOLOGY,
802 Pharmacokinetics). Because reduced renal function is associated with increasing age,
803 AVANDAMET should be used with caution in elderly patients. Care should be taken in dose
804 selection and should be based on careful and regular monitoring of renal function. Generally,
805 elderly patients should not be titrated to the maximum dose of AVANDAMET (see also
806 WARNINGS and DOSAGE AND ADMINISTRATION).

807 **ADVERSE REACTIONS**

808 The incidence and types of adverse events reported in a controlled, 32-week double-blind
809 clinical trial of AVANDAMET in drug-naïve patients (n = 468) are shown in Table 8.

810

811 **Table 8. Adverse Events (>5% in Any Treatment Group) Reported by Drug-Naïve Patients**
 812 **in a 32-week Double-blind Clinical Trial of AVANDAMET**

	AVANDAMET N = 155	Metformin N = 154	Rosiglitazone N = 159
Preferred term	%	%	%
Nausea/vomiting	16	13	8
Diarrhea	14	21	7
Headache	11	12	10
Dyspepsia	10	8	9
Upper respiratory tract infection	9	7	8
Dizziness	8	3	5
Edema	6	3	7
Nasopharyngitis	6	5	4
Abdominal pain	5	6	7
Arthralgia	5	3	7
Loose Stools	5	6	1
Constipation	5	4	6
Influenza	1	2	6

813
 814 The incidence and types of adverse events reported in controlled, 26-week clinical trials of
 815 rosiglitazone maleate administered in combination with metformin hydrochloride 2,500 mg/day
 816 in comparison to adverse reactions reported in association with rosiglitazone and metformin
 817 monotherapies are shown in Table 9. Overall, the types of adverse experiences reported when
 818 rosiglitazone was used in combination with metformin were similar to those reported during
 819 monotherapy with rosiglitazone.
 820

821 **Table 9. Adverse Events (≥5% in Any Treatment Group) Reported by Patients in 26-week**
 822 **Double-blind Clinical Trials of Rosiglitazone Added to Metformin Therapy**

	Rosiglitazone N = 2,526	Placebo N = 601	Metformin N = 225	Rosiglitazone plus metformin N = 338
Preferred term	%	%	%	%
Upper respiratory tract infection	9.9	8.7	8.9	16.0
Injury	7.6	4.3	7.6	8.0
Headache	5.9	5.0	8.9	6.5
Back pain	4.0	3.8	4.0	5.0
Hyperglycemia	3.9	5.7	4.4	2.1
Fatigue	3.6	5.0	4.0	5.9
Sinusitis	3.2	4.5	5.3	6.2
Diarrhea	2.3	3.3	15.6	12.7
Viral infection	3.2	4.0	3.6	5.0
Arthralgia	3.0	4.0	2.2	5.0
Anemia	1.9	0.7	2.2	7.1

823
 824 In the double-blind trial evaluating AVANDAMET in drug-naïve patients, mild (no
 825 intervention required) to moderate (minor intervention required) symptomatic hypoglycemia was
 826 reported by 18/155 (12%) of patients treated with AVANDAMET, 14/154 (9%) with metformin,
 827 and 13/159 (8%) with rosiglitazone. Approximately half of these episodes were accompanied by
 828 a simultaneous capillary glucose measurement, and the rate of confirmed hypoglycemia (blood
 829 glucose ≤50mg/dL) was low in this clinical study: 0.6% (1/155) for AVANDAMET, 1.3%
 830 (2/154) for metformin and 0% with rosiglitazone. No hypoglycemic episode led to withdrawal
 831 with AVANDAMET treatment, and no patients required medical intervention due to
 832 hypoglycemia.

833 Reports of hypoglycemia in patients treated with rosiglitazone added to maximum metformin
 834 therapy in double-blind studies were more frequent (3.0%) than in patients treated with
 835 rosiglitazone (0.6%) or metformin monotherapies (1.3%) or placebo (0.2%). Overall, anemia and
 836 edema were generally mild to moderate in severity and usually did not require discontinuation of
 837 treatment with rosiglitazone.

838 In the double-blind trial in drug-naïve patients, the incidence of edema was 6% on
 839 AVANDAMET compared to 7% on rosiglitazone and 3% on metformin.

840 In the double-blind trial in drug-naïve patients, the incidence of anemia was 4% in patients
 841 treated with AVANDAMET compared to either rosiglitazone (2%) or metformin (0%). Reports
 842 of anemia (7.1%) were greater in patients treated with rosiglitazone added to metformin
 843 compared to monotherapy with rosiglitazone. Lower pre-treatment hemoglobin/hematocrit levels
 844 in patients enrolled in the metformin and rosiglitazone combination therapy clinical trials may

845 have contributed to the higher reporting rate of anemia in these studies (see ADVERSE
846 REACTIONS, Laboratory Abnormalities, *Hematologic*).

847 Edema was reported in 4.8% of patients receiving rosiglitazone compared to 1.3% on placebo,
848 and 2.2% on metformin monotherapy and 4.4% on rosiglitazone in combination with maximum
849 doses of metformin.

850 **Combination with Insulin:** The safety profile for AVANDAMET plus insulin was consistent
851 with that of the individual components (rosiglitazone or metformin) and with that of
852 rosiglitazone used in combination with insulin.

853 The incidence of hypoglycemia (confirmed by fingerstick blood glucose concentration
854 ≤ 50 mg/dL) was 14% for patients on AVANDAMET plus insulin compared to 10% for patients
855 on insulin monotherapy.

856 The incidence of edema was 7% when insulin was added to AVANDAMET compared to 3%
857 with insulin monotherapy. This trial excluded patients with pre-existing heart failure or new or
858 worsening edema on AVANDAMET therapy.

859 However, in 26-week double-blind, fixed-dose studies of rosiglitazone added to insulin,
860 edema was reported with higher frequency (rosiglitazone in combination with insulin, 14.7%;
861 insulin, 5.4%). Reports of new-onset or exacerbation of congestive heart failure occurred at rates
862 of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with
863 rosiglitazone. There were too few events to confirm a dose relationship; however, the incidence
864 of heart failure appeared higher with rosiglitazone 8 mg daily. (See WARNINGS, Rosiglitazone
865 maleate, Cardiac Failure and Other Cardiac Effects.)

866 The incidence of anemia was 2% for AVANDAMET in combination with insulin compared to
867 1% for insulin monotherapy.

868 **Postmarketing Experience:** In addition to adverse reactions reported from clinical trials, the
869 events described below have been identified during post-approval use of AVANDAMET or its
870 individual components. Because these events are reported voluntarily from a population of
871 unknown size, it is not possible to reliably estimate their frequency or to always establish a
872 causal relationship to drug exposure.

873 In postmarketing experience in patients receiving thiazolidinedione therapy, serious adverse
874 events with or without a fatal outcome, potentially related to volume expansion (e.g., congestive
875 heart failure, pulmonary edema, and pleural effusions) have been reported. (See WARNINGS,
876 Rosiglitazone maleate, Cardiac Failure and Other Cardiac Effects.)

877 Rash, pruritus, urticaria, angioedema, anaphylactic reaction, and Stevens-Johnson syndrome
878 have been reported rarely.

879 Reports of new onset or worsening diabetic macular edema with decreased visual acuity have
880 also been received (see PRECAUTIONS, Rosiglitazone maleate, Macular Edema).

881 (See also GLUCOPHAGE prescribing information, ADVERSE REACTIONS.)

882 **Laboratory Abnormalities: Hematologic:** Decreases in mean hemoglobin and hematocrit
883 occurred in a dose-related fashion in adult patients treated with rosiglitazone maleate (mean
884 decreases in individual studies up to 1.0 gram/dL hemoglobin and up to 3.3% hematocrit). The

885 time course and magnitude of decreases were similar in patients treated with a combination of
886 rosiglitazone and other hypoglycemic agents or rosiglitazone monotherapy. Pre-treatment levels
887 of hemoglobin and hematocrit were lower in patients in metformin combination studies and may
888 have contributed to the higher reporting rate of anemia. In a single study in pediatric patients,
889 decreases in hemoglobin and hematocrit (mean decreases of 0.29 g/dL and 0.95%, respectively)
890 were reported with rosiglitazone. White blood cell counts also decreased slightly in adult patients
891 treated with rosiglitazone. Decreases in hematologic parameters may be related to increased
892 plasma volume observed with rosiglitazone treatment.

893 In controlled clinical trials of metformin hydrochloride of 29 weeks' duration, a decrease to
894 subnormal levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations,
895 was observed in approximately 7% of patients. Such a decrease, possibly due to interference with
896 B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with
897 anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂
898 supplementation.

899 **Lipids:** Changes in serum lipids have been observed following treatment with rosiglitazone
900 maleate in adults (see CLINICAL STUDIES). Small changes in serum lipid parameters were
901 reported in children treated with rosiglitazone for 24 weeks.

902 **Serum Transaminase Levels:** In clinical studies in 4,598 patients treated with
903 rosiglitazone maleate encompassing approximately 3,600 patient years of exposure, there was no
904 evidence of drug-induced hepatotoxicity or elevated ALT levels.

905 In controlled trials, 0.2% of patients treated with rosiglitazone maleate had reversible
906 elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on
907 active comparators. Hyperbilirubinemia was found in 0.3% of patients treated with rosiglitazone
908 compared with 0.9% treated with placebo and 1% in patients treated with active comparators.

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

913 In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to
914 hepatic failure. In postmarketing experience with rosiglitazone maleate, reports of hepatic
915 enzyme elevations 3 or more times the upper limit of normal and hepatitis have been received
916 (see PRECAUTIONS, Hepatic Effects).

917 **OVERDOSAGE**

918 **Rosiglitazone maleate:** Limited data are available with regard to overdosage in humans.
919 In clinical studies in volunteers, rosiglitazone has been administered at single oral doses of up to
920 20 mg and was well tolerated. In the event of an overdose, appropriate supportive treatment
921 should be initiated as dictated by the patient's clinical status.

922 **Metformin hydrochloride:** Hypoglycemia has not been seen with ingestion of up to
923 85 grams of metformin hydrochloride, although lactic acidosis has occurred in such

924 circumstances (see WARNINGS). Metformin is dialyzable with a clearance of up to 170 mL/min
925 under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of
926 accumulated metformin from patients in whom metformin overdose is suspected.

927 **DOSAGE AND ADMINISTRATION**

928 **General:** The dosage of antidiabetic therapy with AVANDAMET should be individualized on
929 the basis of effectiveness and tolerability while not exceeding the maximum recommended daily
930 dose of 8 mg/2,000 mg. The risk-benefit of initiating monotherapy versus dual therapy with
931 AVANDAMET should be considered. (See CLINICAL TRIALS, WARNINGS,
932 PRECAUTIONS, and ADVERSE REACTIONS.)

933 All patients should start the rosiglitazone component of AVANDAMET at the lowest
934 recommended dose. Further increases in the dose of rosiglitazone should be accompanied by
935 careful monitoring for adverse events related to fluid retention. (See WARNINGS, Rosiglitazone
936 maleate, Cardiac Failure and Other Cardiac Events.)

937 AVANDAMET is generally given in divided doses with meals, with gradual dose escalation.
938 This reduces gastrointestinal side effects (largely due to metformin) and permits determination of
939 the minimum effective dose for the individual patient.

940 Sufficient time should be given to assess adequacy of therapeutic response. Fasting plasma
941 glucose (FPG) should be used to determine the therapeutic response to AVANDAMET.

942 **AVANDAMET in Drug-Naïve Patients:** The recommended starting dose of AVANDAMET
943 is 2 mg/500 mg administered once or twice daily. For patients with HbA1c >11% or FPG
944 >270 mg/dL, a starting dose of 2 mg/500 mg twice daily may be considered. The dose of
945 AVANDAMET may be increased in increments of 2 mg/500 mg per day to a maximum of 8
946 mg/2,000 mg per day given in divided doses if patients are not adequately controlled after
947 4 weeks.

948 **AVANDAMET in Patients Inadequately Controlled with Rosiglitazone or Metformin
949 Monotherapy:** The selection of the dose of AVANDAMET in patients treated with
950 rosiglitazone and/or metformin therapy should be based on the patient's current doses of
951 rosiglitazone and/or metformin. After an increase in metformin dosage, dose titration is
952 recommended if patients are not adequately controlled after 1 to 2 weeks. After an increase in
953 rosiglitazone dosage, dose titration is recommended if patients are not adequately controlled after
954 8 to 12 weeks.

955 **For patients inadequately controlled on metformin monotherapy,** the usual starting dose
956 of AVANDAMET is 4 mg rosiglitazone (total daily dose) plus the dose of metformin already
957 being taken (see Table 10).

958 **For patients inadequately controlled on rosiglitazone monotherapy,** the usual starting
959 dose of AVANDAMET is 1,000 mg metformin (total daily dose) plus the dose of rosiglitazone
960 already being taken (see Table 10).

961 When switching from combination therapy of rosiglitazone plus metformin as separate tablets,
962 the usual starting dose of AVANDAMET is the dose of rosiglitazone and metformin already
963 being taken.

964 If additional glycemic control is needed, the daily dose of AVANDAMET may be increased
965 by increments of 4 mg rosiglitazone and/or 500 mg metformin, up to the maximum
966 recommended total daily dose of 8 mg/2,000 mg.

967

968 **Table 10. AVANDAMET Starting Dose for Patients Treated with Metformin and/or**
969 **Rosiglitazone**

PRIOR THERAPY	Usual AVANDAMET Starting Dose	
	Tablet strength	Number of tablets
Metformin HCl*		
1,000 mg/day	2 mg/500 mg	1 tablet twice a day
2,000 mg/day	2 mg/1,000 mg	1 tablet twice a day
Rosiglitazone		
4 mg/day	2 mg/500 mg	1 tablet twice a day
8 mg/day	4 mg/500 mg	1 tablet twice a day

970 * For patients on doses of metformin HCl between 1,000 and 2,000 mg/day, initiation of
971 AVANDAMET requires individualization of therapy.

972

973 **Specific Patient Populations: *Pregnancy:*** AVANDAMET is not recommended for use in
974 pregnancy.

975 ***Geriatric:*** The initial and maintenance dosing of AVANDAMET should be conservative in
976 patients with advanced age, due to the potential for decreased renal function in this population.

977 ***Renal Impairment:*** Any dosage adjustment should be based on a careful assessment of
978 renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to
979 the maximum dose of AVANDAMET. Monitoring of renal function is necessary to aid in
980 prevention of metformin-associated lactic acidosis, particularly in the elderly (see WARNINGS).

981 ***Hepatic Impairment:*** Therapy with AVANDAMET should not be initiated if the patient
982 exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT
983 >2.5X upper limit of normal at start of therapy) (see PRECAUTIONS, Hepatic Effects and
984 CLINICAL PHARMACOLOGY, Special Populations, *Hepatic Impairment*). Liver enzyme
985 monitoring is recommended in all patients prior to initiation of therapy with AVANDAMET and
986 periodically thereafter (see PRECAUTIONS, Hepatic Effects).

987 ***Pediatric:*** Safety and effectiveness of AVANDAMET in pediatric patients have not been
988 established. AVANDAMET and rosiglitazone are not indicated for use in pediatric patients.

989 HOW SUPPLIED

990 Tablets: Each tablet contains rosiglitazone as the maleate and metformin hydrochloride as
991 follows:

992 2 mg/500 mg – pale pink, film-coated oval tablet, debossed with gsk on one side and 2/500 on
993 the other.

994 4 mg/500 mg – orange, film-coated oval tablet, debossed with gsk on one side and 4/500 on
995 the other.

996 2 mg/1,000 mg – yellow, film-coated oval tablet, debossed with gsk on one side and 2/1000
997 on the other.

998 4 mg/1,000 mg – pink, film-coated oval tablet, debossed with gsk on one side and 4/1000 on
999 the other.

1000

1001 2 mg/500 mg bottles of 60: NDC 0007-3167-18

1002 4 mg/500 mg bottles of 60: NDC 0007-3168-18

1003 2 mg/1,000 mg bottles of 60: NDC 0007-3163-18

1004 4 mg/1,000 mg bottles of 60: NDC 0007-3164-18

1005 **STORAGE**

1006 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

1007 Dispense in a tight, light-resistant container.

1008 **REFERENCE**

1009 1. Park JY, Kim KA, Kang MH, et al. Effect of rifampin on the pharmacokinetics of
1010 rosiglitazone in healthy subjects. *Clin Pharmacol Ther* 2004;75:157-162.

1011

1012 GLUCOPHAGE is a registered trademark of Merck Santé S.A.S., an associate of Merck KGaA
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1016 GlaxoSmithKline

1017 Research Triangle Park, NC 27709

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1022

1023 April 2007

AT:LFS-019

1024 PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

1025

1026

1027

PATIENT INFORMATION LEAFLET

1028

AVANDAMET® (ah-VAN-duh-met)

1029

Rosiglitazone Maleate and Metformin Hydrochloride Tablets

1030

Read this information carefully before you start taking AVANDAMET and read the information

1031

you get each time you get more AVANDAMET. There may be new information. This

1032

information does not take the place of talking with your doctor about your medical condition or

1033

your treatment. If you have any questions about AVANDAMET, ask your doctor. Only your

1034

doctor can determine if AVANDAMET is right for you.

1035

What is AVANDAMET?

1036

AVANDAMET is a medicine used, along with diet and exercise, to treat type 2 (“adult-onset”)

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diabetes (“high sugar”). This is also called non-insulin-dependent diabetes mellitus. People who

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have type 2 diabetes do not make enough insulin or do not respond normally to the insulin their

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bodies make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious

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medical problems including kidney damage, amputation and blindness. Diabetes is also closely

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linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a

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normal level. Studies have shown that controlling blood sugar may help prevent or delay

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complications of diabetes such as heart disease, kidney disease or blindness.

1044

High blood sugar can be lowered by diet and exercise, by a number of medicines taken by

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mouth, and by insulin shots. AVANDAMET combines two sugar- (glucose) lowering medicines,

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rosiglitazone and metformin, in one tablet. Metformin works mainly by decreasing the

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production of sugar by your liver. Rosiglitazone helps your body respond better to its natural

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insulin and does not cause your body to make more insulin. These medicines work together to

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help control your blood sugar.

1050

Before you take AVANDAMET, you should first try to control your diabetes by diet and

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exercise. In order for AVANDAMET to be most effective, you should continue to exercise and

1052

follow the diet recommended for your diabetes even while taking AVANDAMET.

1053

WARNING: A small number of people who have taken metformin, one of the two drugs

1054

that make up AVANDAMET, have developed a serious condition called lactic acidosis.

1055

Lactic acidosis is caused by a build-up of lactic acid in the blood. Lactic acidosis happens

1056

most often in people with kidney problems. People with kidney problems should not take

1057

AVANDAMET. (see “What are the side effects of AVANDAMET?”)

1058

Who should not take AVANDAMET?

1059

Some conditions increase your chance of getting lactic acidosis, or cause other problems if you

1060

take AVANDAMET. Your risk of getting lactic acidosis is very low as long as your kidneys and

1061

liver are healthy. Most of the conditions listed below can increase your chance of getting lactic

1062

acidosis or cause other problems if you take AVANDAMET.

- 1063 Do not take AVANDAMET if you:
- 1064 • Had liver problems while taking REZULIN[®] (troglitazone), another medicine for diabetes.
 - 1065 • Have kidney or liver problems. Before you take AVANDAMET and while you take it,
1066 your doctor should test your blood to check for signs of kidney or liver problems.
 - 1067 • Have heart failure, until you talk with your doctor. Rosiglitazone, one drug in
1068 AVANDAMET, may cause fluid retention (swelling or edema), alone or in combination
1069 with other diabetes medicines. Fluid retention can lead to heart failure or make heart failure
1070 worse. **Call your doctor if you have shortness of breath or a sudden weight change.**
 - 1071 • Drink a lot of alcohol (all the time or short binge drinking).
 - 1072 • Are seriously dehydrated (as when your body has lost a lot of water from diarrhea or
1073 vomiting).
 - 1074 • Are going to have an x-ray procedure with an injection of dyes (contrast agents) in your
1075 vein with a needle. Talk to your doctor about when to stop AVANDAMET and when to
1076 start it again.
 - 1077 • Are scheduled to have surgery or an operation. Talk to your doctor about when to stop
1078 AVANDAMET and when to start it again.
 - 1079 • Develop a serious condition such as a heart attack, severe infection, or a stroke.
 - 1080 • Are 80 years or older and have NOT had your kidney function tested.
 - 1081 • Have had an allergic reaction to AVANDIA[®] (rosiglitazone) or metformin (e.g.,
1082 GLUCOPHAGE[®]).
 - 1083 • Have type 1 (“juvenile”) diabetes or a history of metabolic ketoacidosis, including diabetic
1084 ketoacidosis.
 - 1085 • Have a type of diabetic eye disease called macular edema (swelling of the back of the eye)
1086 until you talk to your doctor.

1087 **Can AVANDAMET be used in nursing or pregnant women or in children?**

1088 Tell your doctor if you are pregnant, plan to become pregnant, or if you are nursing a child. If
1089 you are a premenopausal woman (before the “change of life”), who is not having periods
1090 regularly or at all, you may need to consider birth control options since AVANDAMET may
1091 increase your chances of becoming pregnant. Talk with your doctor about your choices.
1092 AVANDAMET has not been studied in children. AVANDAMET is not recommended for use in
1093 children.

1094 **How should I take AVANDAMET?**

1095 AVANDAMET should be taken by mouth and with meals. AVANDAMET should be taken
1096 twice a day to help improve blood sugar levels. Your doctor may need to adjust your dose until
1097 your blood sugar is better controlled.

1098 While you are taking AVANDAMET, you should also follow recommendations of your
1099 healthcare professional for appropriate diet and exercise. Diet and exercise can help your body
1100 use blood sugar better. Test your blood sugar regularly as your doctor tells you.
1101 AVANDAMET can begin to work 1 or 2 weeks after you start taking it. It may take 2-3 months
1102 to see the full effect.
1103 Your doctor should check your eyes regularly. Very rarely, some patients have experienced
1104 vision changes due to swelling in the back of the eye while taking rosiglitazone, one of the drugs
1105 in AVANDAMET.
1106 While taking AVANDAMET tell your doctor if you:

- 1107 • Have an illness that causes severe vomiting, diarrhea or fever, or if you drink a much lower
1108 amount of liquid than normal. These conditions can lead to severe dehydration (loss of
1109 water from your body). You may need to stop taking AVANDAMET for a short time.
- 1110 • Plan to have surgery or an x-ray procedure with injection of dye (contrast agent). You may
1111 need to stop taking AVANDAMET for a short time.
- 1112 • Start to take other medicines (including non-prescription and dietary or herbal
1113 supplements) or change how you take a medicine. AVANDAMET may affect how well
1114 other drugs work, and some drugs may affect how well AVANDAMET works. Some
1115 medicines may cause high blood sugar or low blood sugar.

1116 **What should I avoid while taking AVANDAMET?**

1117 Avoid drinking a lot of alcoholic drinks while taking AVANDAMET. This means you should
1118 not binge drink for short periods, and you should not drink a lot of alcohol on a regular basis.
1119 Drinking a lot of alcohol can increase the chance of getting lactic acidosis.

1120 **What are the possible side effects of AVANDAMET?**

1121 **In rare cases, metformin, one of the drugs in AVANDAMET, can cause a serious side effect**
1122 **called lactic acidosis. This is caused by a build-up of lactic acid in your blood. This build-up**
1123 **can cause serious damage. Lactic acidosis is a medical emergency that must be treated in a**
1124 **hospital.** Lactic acidosis is rare and has occurred mostly in people whose kidneys were not
1125 working normally. Lactic acidosis has been reported in about 1 in 33,000 patients taking
1126 metformin over the course of a year. Although rare, if lactic acidosis does occur, it can be fatal in
1127 up to half the people who develop it. Call your doctor right away if you have signs of lactic
1128 acidosis such as:

- 1129 • feeling very weak, tired, or uncomfortable (malaise)
- 1130 • unusual muscle pain
- 1131 • unusual sleepiness
- 1132 • rapid breathing that you can't explain
- 1133 • unusual or unexpected stomach problems (such as nausea or vomiting)
- 1134 • low body temperature

1135 • feeling dizzy or light-headed

1136 • suddenly having a slow or uneven heartbeat

1137 It is important for your liver to be working normally when you take AVANDAMET. Your liver
1138 helps remove lactic acid from your blood. Before you take AVANDAMET, your doctor will test
1139 your blood to check for signs of liver problems. Sometimes after you start taking it, your doctor
1140 may recheck your blood. Very rarely, serious liver problems have been reported with
1141 rosiglitazone, one of the drugs in AVANDAMET. Call your doctor right away if you have
1142 unexplained symptoms such as:

1143 • nausea or vomiting

1144 • stomach pain

1145 • unusual or unexplained tiredness

1146 • loss of appetite

1147 • dark urine

1148 • yellowing of your skin or the whites of your eyes

1149 AVANDAMET may cause fluid retention or swelling, which could lead to heart failure or make
1150 heart failure worse, so tell your doctor if you have a history of heart failure or swelling (edema).

1151 Call your doctor right away if you have symptoms such as:

1152 • swelling or fluid retention, especially of the ankles or legs

1153 • shortness of breath or trouble breathing, especially when you lie down

1154 • unusual tiredness

1155 • an unusually rapid increase in weight

1156 There is a small risk of developing low blood sugar (hypoglycemia) while taking
1157 AVANDAMET. Lightheadedness, dizziness, shakiness or hunger may indicate that your blood
1158 sugar is too low. This can happen if you skip meals, if you use another medicine that lowers
1159 blood sugar, or if you have certain medical problems.

1160 *Other Side Effects.* Common side effects of AVANDAMET are diarrhea, nausea, and upset
1161 stomach. These side effects usually occur during the first few weeks of therapy. Taking
1162 AVANDAMET with meals can help reduce these side effects. Stomach problems when you first
1163 take AVANDAMET are common. However, stomach problems that start up later may be a sign
1164 of something more serious and should be discussed with your doctor. Other common side effects
1165 are cold-like symptoms, headache, weight gain, and anemia.

1166 **How should I store AVANDAMET?**

1167 AVANDAMET should be stored at room temperature in a childproof container out of the reach
1168 of children. Store AVANDAMET in its original container.

1169 **General Advice about prescription medicines**
1170 This leaflet summarizes important information about AVANDAMET. If you have questions or
1171 problems, talk with your doctor or other healthcare provider. You can ask your doctor or
1172 pharmacist for information about AVANDAMET that is written for healthcare providers.
1173 Medicines are sometimes prescribed for purposes other than those listed in a patient information
1174 leaflet. Do not use AVANDAMET for a condition for which it was not prescribed. Do not share
1175 your medicine with other people.
1176



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