

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

AVANDAMET (rosiglitazone maleate and metformin hydrochloride) Tablets

Initial U.S. Approval: 2002

WARNINGS

See full prescribing information for complete boxed warning.

Rosiglitazone maleate: CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION

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

Metformin hydrochloride: LACTIC ACIDOSIS

- **Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment and acute congestive heart failure. (5.1)**
- **Symptoms include malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. (5.1)**
- **If acidosis is suspected, discontinue AVANDAMET and hospitalize the patient immediately. (5.1)**

RECENT MAJOR CHANGES

Boxed Warning	02/2011
Indications and Usage (1)	02/2011
Dosage and Administration (2)	02/2011
Warnings and Precautions, Cardiac Failure (5.2)	02/2011
Warnings and Precautions, Major Adverse Cardiovascular Events (5.3)	02/2011
Warnings and Precautions, Rosiglitazone REMS Program (5.4)	XX/2011
Warnings and Precautions, Fractures (5.9)	02/2011

INDICATIONS AND USAGE

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

- already taking rosiglitazone, or
- not already taking rosiglitazone and are unable to achieve glycemic

control on other diabetes medications and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS) or pioglitazone-containing products (ACTOPLUS MET®, ACTOPLUS MET XR®, DUETACT®) for medical reasons. (1)

Other Important Limitations of Use:

- Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. (1)
- Coadministration with insulin is not recommended. (1, 5.2, 5.3)

DOSAGE AND ADMINISTRATION

- Individualize the starting dose based on the patient's current regimen. (2.1)
- Dose increases should be accompanied by careful monitoring for adverse events related to fluid retention. (2.1)
- Give in divided doses with meals with gradual dose escalation to reduce the gastrointestinal side effects. (2.2)
- Do not exceed the maximum recommended daily dose of 8 mg rosiglitazone and 2,000 mg metformin. (2.3)
- Do not initiate if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels. (2.4)

DOSAGE FORMS AND STRENGTHS

Oval, film-coated tablets containing rosiglitazone/metformin hydrochloride: 2 mg/500 mg, 4 mg/500 mg, 2 mg/1,000 mg, and 4 mg/1,000 mg (3)

CONTRAINDICATIONS

- Initiation in patients with established NYHA Class III or IV heart failure. (4)
- Use in significant renal disease or renal dysfunction. (4)
- Use in acute or chronic metabolic acidosis. (4)
- Use in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials. (4, 5.1)

WARNINGS AND PRECAUTIONS

- Fluid retention, which may exacerbate or lead to heart failure, may occur. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk of other cardiovascular effects. (5.2)
- Increased risk of myocardial infarction has been observed in a meta-analysis of 52 clinical trials of rosiglitazone (incidence rate 0.4% versus 0.3%). (5.3)
- Coadministration with insulin is not recommended. (1, 5.2, 5.3)
- Assess renal function before starting therapy and at least annually. (5.1)
- Avoid use in patients with evidence of hepatic disease. (2.4, 5.1)
- Warn patients against excessive alcohol intake. (5.1)
- Promptly evaluate patients who develop laboratory abnormalities or clinical illness for evidence of ketoacidosis or lactic acidosis. (5.1)
- Dose-related edema (5.5), weight gain (5.6), and anemia (5.10) may occur.
- Macular edema has been reported. (5.8)
- Increased incidence of bone fracture. (5.9)
- Measure hematologic parameters annually. (5.10)

ADVERSE REACTIONS

The most common adverse reactions (≥10%) include nausea/vomiting, diarrhea, headache, and dyspepsia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Inhibitors of CYP2C8 (e.g., gemfibrozil) may increase rosiglitazone levels. (7.1)
- Inducers of CYP2C8 (e.g., rifampin) may decrease rosiglitazone levels. (7.1)
- Cationic drugs eliminated by renal tubular secretion; use with caution. (7.2)

USE IN SPECIFIC POPULATIONS

- Do not use during pregnancy. No human or animal data. (8.1)
- Safety and effectiveness in children under 18 years have not been established. (8.4)
- Because reduced renal function is associated with increasing age, use with caution in elderly patients. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: XX/2011

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1 **FULL PRESCRIBING INFORMATION**

2 **WARNINGS**

3 ***Rosiglitazone maleate*: CONGESTIVE HEART FAILURE AND MYOCARDIAL**
4 **INFARCTION**

- 5 • Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in
6 some patients [*see Warnings and Precautions (5.2)*]. After initiation of AVANDAMET, and
7 after dose increases, observe patients carefully for signs and symptoms of heart failure
8 (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and
9 symptoms develop, the heart failure should be managed according to current standards of
10 care. Furthermore, discontinuation or dose reduction of AVANDAMET must be considered.
- 11 • AVANDAMET is not recommended in patients with symptomatic heart failure. Initiation of
12 AVANDAMET in patients with established NYHA Class III or IV heart failure is
13 contraindicated. [*See Contraindications (4) and Warnings and Precautions (5.2).*]
- 14 • A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of
15 which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an
16 increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067
17 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or
18 placebo, showed a statistically non-significant increased risk of myocardial infarction, and a
19 statistically non-significant decreased risk of death. There have been no clinical trials directly
20 comparing cardiovascular risk of rosiglitazone and ACTOS[®] (pioglitazone, another
21 thiazolidinedione), but in a separate trial, pioglitazone (when compared to placebo) did not
22 show an increased risk of myocardial infarction or death. [*See Warnings and Precautions*
23 *(5.3).*]
- 24 • Because of the potential increased risk of myocardial infarction, AVANDAMET is available
25 only through a restricted distribution program called the AVANDIA-Rosiglitazone
26 Medicines Access Program. Both prescribers and patients need to enroll in the program. To
27 enroll, call 1-800-AVANDIA or visit www.AVANDIA.com. [*See Warnings and Precautions*
28 *(5.4).*]

29 ***Metformin hydrochloride*: LACTIC ACIDOSIS**

- 30 • Lactic acidosis is a rare, but serious complication that can occur due to metformin
31 accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol
32 intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. [*See*
33 *Warnings and Precautions (5.1).*]
- 34 • Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and
35 nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion
36 gap and elevated blood lactate. [*See Warnings and Precautions (5.1).*]

- 37 • If acidosis is suspected, discontinue AVANDAMET and hospitalize the patient immediately
38 [see *Warnings and Precautions (5.1)*].

39 1 INDICATIONS AND USAGE

40 After consultation with a healthcare professional who has considered and advised the
41 patient of the risks and benefits of rosiglitazone, AVANDAMET[®] is indicated as an adjunct to
42 diet and exercise to improve glycemic control when treatment with both rosiglitazone and
43 metformin is appropriate in adults with type 2 diabetes mellitus who either are:

- 44 • already taking rosiglitazone, or
45 • not already taking rosiglitazone and unable to achieve glycemic control on other diabetes
46 medications and, in consultation with their healthcare provider, have decided not to take
47 pioglitazone (ACTOS[®]) or pioglitazone-containing products (ACTOPLUS MET[®],
48 ACTOPLUS MET XR[®], DUETACT[®]) for medical reasons.

49 Other Important Limitations of Use:

- 50 • Due to its mechanism of action, rosiglitazone is active only in the presence of endogenous
51 insulin. Therefore, AVANDAMET should not be used in patients with type 1 diabetes.
52 • Coadministration of AVANDAMET with insulin is not recommended [see *Warnings and*
53 *Precautions (5.2, 5.3)*].

54 2 DOSAGE AND ADMINISTRATION

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

58 2.1 Starting Dose

59 AVANDAMET is generally given in divided doses with meals.

60 All patients should start the rosiglitazone component of AVANDAMET at the lowest
61 recommended dose. Further increases in the dose of rosiglitazone should be accompanied by
62 careful monitoring for adverse events related to fluid retention [see **Boxed Warning and**
63 *Warnings and Precautions (5.5)*].

64 If therapy with a combination tablet containing rosiglitazone and metformin is considered
65 appropriate for a patient with type 2 diabetes mellitus, then the selection of the dose of
66 AVANDAMET should be based on the patient's current doses of rosiglitazone and/or
67 metformin.

68 **To switch to AVANDAMET for patients currently treated with metformin**, the usual
69 starting dose of AVANDAMET is 4 mg rosiglitazone (total daily dose) plus the dose of
70 metformin already being taken (see Table 1).

71 **To switch to AVANDAMET for patients currently treated with rosiglitazone**, the
72 usual starting dose of AVANDAMET is 1,000 mg metformin (total daily dose) plus the dose of
73 rosiglitazone already being taken (see Table 1).

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

77
78 Table 1. AVANDAMET Starting Dose for Patients Treated with Metformin and/or
79 Rosiglitazone

PRIOR THERAPY	Usual AVANDAMET Starting Dose		
	Total daily dose	Tablet strength	Number of tablets
Metformin ^a			
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	

80 ^a For patients on doses of metformin between 1,000 and 2,000 mg/day, initiation of
81 AVANDAMET requires individualization of therapy.

82
83 **2.2 Dose Titration**

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

87 Sufficient time should be given to assess adequacy of therapeutic response. FPG should
88 be used initially to determine the therapeutic response to AVANDAMET. If additional glycemic
89 control is needed, the daily dose of AVANDAMET may be increased by increments of 4 mg
90 rosiglitazone and/or 500 mg metformin.

91 After an increase in metformin dosage, dose titration is recommended if patients are not
92 adequately controlled after 1 to 2 weeks. After an increase in rosiglitazone dosage, dose titration
93 is recommended if patients are not adequately controlled after 8 to 12 weeks.

94 **2.3 Maximum Dose**

95 The maximum recommended total daily dose of AVANDAMET is 8 mg rosiglitazone
96 (taken as 4 mg twice daily) and 2,000 mg metformin (taken as 1,000 mg twice daily).

97 **2.4 Specific Patient Populations**

98 Renal Impairment: Any dosage adjustment should be based on a careful assessment of
99 renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to
100 the maximum dose of AVANDAMET. Monitoring of renal function is necessary to aid in
101 prevention of metformin-associated lactic acidosis, particularly in the elderly [*see Warnings and*
102 *Precautions (5.1)*].

103 Hepatic Impairment: Liver enzymes should be measured prior to initiating treatment
104 with AVANDAMET. Therapy with AVANDAMET should not be initiated if the patient exhibits

105 clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X
106 upper limit of normal at start of therapy). After initiation of AVANDAMET, liver enzymes
107 should be monitored periodically per the clinical judgment of the healthcare professional [*see*
108 *Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)*].

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

111 Pediatric: Safety and effectiveness of AVANDAMET in pediatric patients have not been
112 established. AVANDAMET and rosiglitazone are not recommended for use in pediatric patients.

113 Pregnancy: AVANDAMET is not recommended for use in pregnancy.

114 **3 DOSAGE FORMS AND STRENGTHS**

115 Each film-coated oval tablet contains rosiglitazone as the maleate and metformin
116 hydrochloride as follows:

- 117 • 2 mg/500 mg – pale pink, debossed with gsk on one side and 2/500 on the other
- 118 • 4 mg/500 mg – orange, debossed with gsk on one side and 4/500 on the other
- 119 • 2 mg/1,000 mg – yellow, debossed with gsk on one side and 2/1000 on the other
- 120 • 4 mg/1,000 mg – pink, debossed with gsk on one side and 4/1000 on the other

121 **4 CONTRAINDICATIONS**

- 122 • Initiation in patients with established New York Heart Association (NYHA) Class III or IV
123 heart failure [*see **Boxed Warning***].
- 124 • Use in patients with renal disease or renal dysfunction (e.g., as suggested by serum creatinine
125 levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females], or abnormal creatinine clearance), which
126 may also result from conditions such as cardiovascular collapse (shock), acute myocardial
127 infarction, and septicemia [*see **Warnings and Precautions (5.1)***].
- 128 • Use in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with
129 or without coma.
- 130 • Use in patients undergoing radiologic studies involving intravascular administration of
131 iodinated contrast materials, because use of such products may result in acute alteration of
132 renal function. AVANDAMET should be temporarily discontinued in these patients. [*See*
133 *Warnings and Precautions (5.1)*.]

134 **5 WARNINGS AND PRECAUTIONS**

135 **5.1 Lactic Acidosis**

136 Incidence and Management: Lactic acidosis is a rare, but serious, metabolic
137 complication that can occur due to metformin accumulation during treatment with
138 AVANDAMET; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may
139 also occur in association with a number of pathophysiologic conditions, including diabetes
140 mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis
141 is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte
142 disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When

143 metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 mcg/mL are
144 generally found.

145 The reported incidence of lactic acidosis in patients receiving metformin is very low
146 (approximately 0.03 cases/1,000 patient years of exposure, with approximately 0.015 fatal
147 cases/1,000 patient years of exposure). Reported cases have occurred primarily in diabetic
148 patients with significant renal insufficiency, including both intrinsic renal disease and renal
149 hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and
150 multiple concomitant medications. Patients with congestive heart failure requiring
151 pharmacologic management, in particular those with unstable or acute congestive heart failure
152 who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk
153 of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of
154 lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function
155 in patients taking AVANDAMET and by use of the minimum effective dose of AVANDAMET.
156 In particular, treatment of the elderly should be accompanied by careful monitoring of renal
157 function. Treatment with AVANDAMET should not be initiated in patients ≥ 80 years of age
158 unless measurement of creatinine clearance demonstrates that renal function is not reduced, as
159 these patients are more susceptible to developing lactic acidosis. In addition, AVANDAMET
160 should be promptly withheld in the presence of any condition associated with hypoxemia,
161 dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to
162 clear lactate, AVANDAMET should generally be avoided in patients with clinical or laboratory
163 evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either
164 acute or chronic, when taking AVANDAMET, since alcohol potentiates the effects of metformin
165 on lactate metabolism. In addition, AVANDAMET should be temporarily discontinued prior to
166 any intravascular radiocontrast study and for any surgical procedure.

167 The onset of lactic acidosis often is subtle, and accompanied only by nonspecific
168 symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and
169 nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant
170 bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be
171 aware of the possible importance of such symptoms and the patient should be instructed to notify
172 the physician immediately if they occur. AVANDAMET should be withdrawn until the situation
173 is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels,
174 and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of
175 AVANDAMET, gastrointestinal symptoms, which are common during initiation of therapy, are
176 unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic
177 acidosis or other serious disease.

178 Levels of fasting venous plasma lactate above the upper limit of normal but less than
179 5 mmol/L in patients taking AVANDAMET do not necessarily indicate impending lactic
180 acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or
181 obesity, vigorous physical activity or technical problems in sample handling.

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

184 Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a
185 patient with lactic acidosis who is taking AVANDAMET, the drug should be discontinued
186 immediately and general supportive measures promptly instituted. Because metformin is
187 dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt
188 hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.
189 Such management often results in prompt reversal of symptoms and recovery [see
190 *Contraindications (4)*].

191 **Factors That May Predispose Patients to Lactic Acidosis: Assessment of Renal**
192 ***Function:*** Metformin is known to be substantially excreted by the kidney, and the risk of
193 metformin accumulation and lactic acidosis increases with the degree of impairment of renal
194 function. Thus, patients with serum creatinine levels above the upper limit of normal for their
195 age should not receive AVANDAMET. In patients with advanced age, AVANDAMET should
196 be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging
197 is associated with reduced renal function. [See *Dosage and Administration (2.4)* and *Use in*
198 *Specific Populations (8.5)*.]

199 Before initiation of therapy with AVANDAMET and at least annually thereafter, renal
200 function should be assessed and verified as normal. In patients in whom development of renal
201 dysfunction is anticipated, renal function should be assessed more frequently and
202 AVANDAMET discontinued if evidence of renal impairment is present.

203 ***Medications That Affect Renal Function:*** Concomitant medication(s) that may affect
204 renal function or result in significant hemodynamic change or may interfere with the disposition
205 of metformin, such as cationic drugs that are eliminated by renal tubular secretion [see *Drug*
206 *Interactions (7.2)* and *Clinical Pharmacology (12.4)*], should be used with caution.

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

211 ***Radiologic Studies With Intravascular Iodinated Contrast Materials:*** Intravascular
212 contrast studies with iodinated materials can lead to acute alteration of renal function and have
213 been associated with lactic acidosis in patients receiving metformin [see *Contraindications (4)*].
214 Therefore, in patients in whom any such study is planned, AVANDAMET should be temporarily
215 discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the
216 procedure and reinstated only after renal function has been re-evaluated and found to be
217 normal.

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

222 *Alcohol Intake:* Alcohol potentiates the effect of metformin on lactate metabolism.
223 Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while
224 receiving AVANDAMET.

225 *Change in Clinical Status of Patients With Previously Controlled Diabetes:* A
226 patient with type 2 diabetes previously well-controlled on AVANDAMET who develops
227 laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should
228 be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include
229 serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and
230 metformin levels. If acidosis of either form occurs, AVANDAMET must be stopped
231 immediately and other appropriate corrective measures initiated.

232 *[See also Warnings and Precautions (5.7).]*

233 **5.2 Cardiac Failure**

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

240 Patients with congestive heart failure (CHF) NYHA Class I and II treated with
241 rosiglitazone have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-
242 controlled echocardiographic trial was conducted in 224 patients with type 2 diabetes mellitus
243 and NYHA Class I or II CHF (ejection fraction $\leq 45\%$) on background antidiabetic and CHF
244 therapy. An independent committee conducted a blinded evaluation of fluid-related events
245 (including congestive heart failure) and cardiovascular hospitalizations according to predefined
246 criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were
247 reported by investigators. Although no treatment difference in change from baseline of ejection
248 fractions was observed, more cardiovascular adverse events were observed with rosiglitazone
249 treatment compared to placebo during the 52-week trial. (See Table 2.)
250

251 Table 2. Emergent Cardiovascular Adverse Events in Patients With Congestive Heart
252 Failure (NYHA Class I and II) Treated With Rosiglitazone or Placebo (in Addition to
253 Background Antidiabetic and CHF Therapy)

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

254 ^a Includes hospitalization for any cardiovascular reason.
255

256 Initiation of AVANDAMET in patients with established NYHA Class III or IV heart
257 failure is contraindicated. AVANDAMET is not recommended in patients with symptomatic
258 heart failure. [See **Boxed Warning.**]

259 Patients experiencing acute coronary syndromes have not been studied in controlled
260 clinical trials. In view of the potential for development of heart failure in patients having an acute
261 coronary event, initiation of AVANDAMET is not recommended for patients experiencing an
262 acute coronary event, and discontinuation of AVANDAMET during this acute phase should be
263 considered.

264 Patients with NYHA Class III and IV cardiac status (with or without CHF) have not been
265 studied in controlled clinical trials. AVANDAMET is not recommended in patients with NYHA
266 Class III and IV cardiac status.

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

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

271 In 7 controlled, randomized, double-blind trials which had durations from 16 to 26 weeks
272 and which were included in a meta-analysis¹ [see *Warnings and Precautions (5.3)*], patients with
273 type 2 diabetes mellitus were randomized to coadministration of rosiglitazone and insulin

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

280 Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing
281 Rosiglitazone to Pioglitazone: Three observational studies²⁻⁴ in elderly diabetic patients (age
282 65 years and older) found that rosiglitazone statistically significantly increased the risk of
283 hospitalized heart failure compared to use of pioglitazone. One other observational study⁵ in
284 patients with a mean age of 54 years, which also included an analysis in a subpopulation of
285 patients >65 years of age, found no statistically significant increase in emergency department
286 visits or hospitalization for heart failure in patients treated with rosiglitazone compared to
287 pioglitazone in the older subgroup.

288 **5.3 Major Adverse Cardiovascular Events**

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

291 Meta-Analysis of Major Adverse Cardiovascular Events in a Group of 52 Clinical
292 Trials: A meta-analysis was conducted retrospectively to assess cardiovascular adverse events
293 reported across 52 double-blind, randomized, controlled clinical trials (mean duration 6
294 months).¹ These trials had been conducted to assess glucose-lowering efficacy in type 2 diabetes.
295 Prospectively planned adjudication of cardiovascular events did not occur in most of the trials.
296 Some trials were placebo-controlled and some used active oral antidiabetic drugs as controls.
297 Placebo-controlled trials included monotherapy trials (monotherapy with rosiglitazone versus
298 placebo monotherapy) and add-on trials (rosiglitazone or placebo, added to sulfonylurea,
299 metformin, or insulin). Active control trials included monotherapy trials (monotherapy with
300 rosiglitazone versus sulfonylurea or metformin monotherapy) and add-on trials (rosiglitazone
301 plus sulfonylurea or rosiglitazone plus metformin, versus sulfonylurea plus metformin). A total
302 of 16,995 patients were included (10,039 in treatment groups containing rosiglitazone, 6,956 in
303 comparator groups), with 5,167 patient-years of exposure to rosiglitazone and 3,637 patient-
304 years of exposure to comparator. Cardiovascular events occurred more frequently for patients
305 who received rosiglitazone than for patients who received comparators (see Table 3).

306

307

Table 3. Occurrence of Cardiovascular Events in a Meta-Analysis of 52 Clinical Trials

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

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

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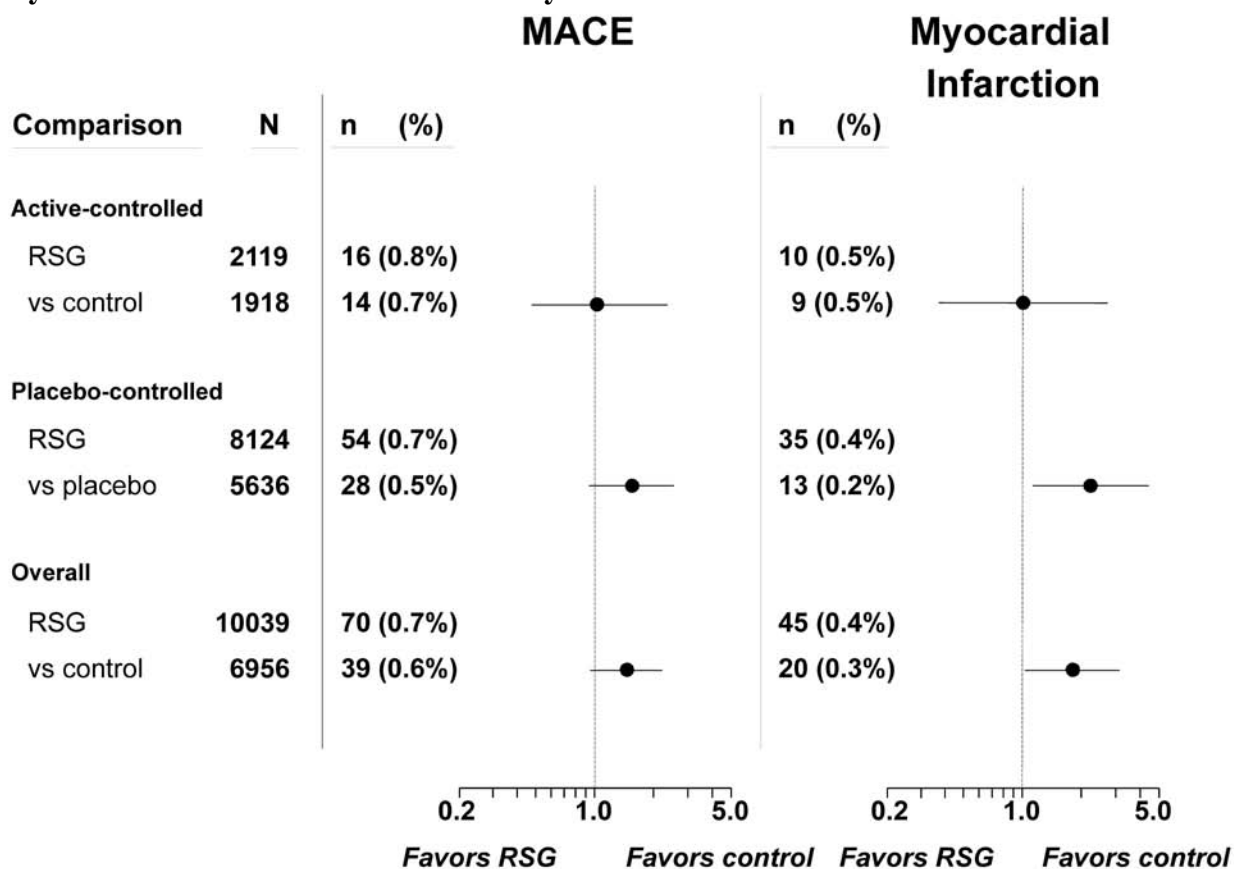
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In this analysis, a statistically significant increased risk of myocardial infarction with rosiglitazone versus pooled comparators was observed. Analyses were performed using a composite of major adverse cardiovascular events (myocardial infarction, stroke, and cardiovascular death), referred to hereafter as MACE. Rosiglitazone had a statistically non-significant increased risk of MACE compared to the pooled comparators. A statistically significant increased risk of myocardial infarction and statistically non-significant increased risk of MACE with rosiglitazone was observed in the placebo-controlled trials. In the active-controlled trials, there was no increased risk of myocardial infarction or MACE. (See Figure 1 and Table 4.)

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



RSG = rosiglitazone

324 **Table 4. Occurrence of MACE and Myocardial Infarction in a Meta-Analysis of 52 Clinical**
325 **Trials by Trial Type**
326
327

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

RSG = rosiglitazone

328
329
330 Of the placebo-controlled trials in the meta-analysis, 7 trials had patients randomized to
331 rosiglitazone plus insulin or insulin. There were more patients in the rosiglitazone plus insulin

332 group compared to the insulin group with myocardial infarctions, MACE, cardiovascular deaths,
333 and all-cause deaths (see Table 5). The total number of patients with stroke was 5 (0.5%) and 4
334 (0.5%) in the rosiglitazone plus insulin and insulin groups, respectively. The use of rosiglitazone
335 in combination with insulin may increase the risk of myocardial infarction [See Warnings and
336 *Precautions (5.1).*]

337

338 **Table 5. Occurrence of Cardiovascular Events for Rosiglitazone in Combination With**
339 **Insulin in a Meta-Analysis of 52 Clinical Trials**

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

340 ND = not defined

341 ^a Events are not exclusive: i.e., a patient with a cardiovascular death due to a myocardial
342 infarction would be counted in 4 event categories (myocardial infarction; myocardial
343 infarction, cardiovascular death, or stroke; cardiovascular death; all-cause death).

344

345 Myocardial Infarction Events in Large, Long-Term, Prospective, Randomized,
346 Controlled Trials of Rosiglitazone: Data from 3 large, long-term, prospective, randomized,
347 controlled clinical trials of rosiglitazone were assessed separately from the meta-analysis.⁶⁻⁸
348 These 3 trials included a total of 14,067 patients (treatment groups containing rosiglitazone
349 N = 6,311; comparator groups N = 7,756), with patient-year exposure of 24,534 patient-years for
350 rosiglitazone and 28,882 patient-years for comparator. Patient populations in the trials included
351 patients with impaired glucose tolerance, patients with type 2 diabetes who were initiating oral
352 agent monotherapy, and patients with type 2 diabetes who had failed monotherapy and were
353 initiating dual oral agent therapy. Duration of follow-up exceeded 3 years in each trial.

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

356 In a long-term, randomized, placebo-controlled, 2x2 factorial trial intended to evaluate
357 rosiglitazone, and separately ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on
358 progression to overt diabetes in 5,269 subjects with glucose intolerance, the incidence of
359 myocardial infarction was higher in the subset of subjects who received rosiglitazone in
360 combination with ramipril than among subjects who received ramipril alone but not in the subset
361 of subjects who received rosiglitazone alone compared to placebo.⁶ The higher incidence of
362 myocardial infarction among subjects who received rosiglitazone in combination with ramipril

363 was not confirmed in the two other large (total N = 8,798) long-term, randomized, active-
364 controlled clinical trials conducted in patients with type 2 diabetes, in which 30% and 40% of
365 patients in the two trials reported angiotensin-converting enzyme inhibitor use at baseline.^{7,8}

366 There have been no adequately designed clinical trials directly comparing rosiglitazone to
367 pioglitazone on cardiovascular risks. However, in a long-term, randomized, placebo-controlled
368 cardiovascular outcomes trial comparing pioglitazone to placebo in patients with type 2 diabetes
369 mellitus and prior macrovascular disease, pioglitazone was not associated with an increased risk
370 of myocardial infarction or total mortality.⁹

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

376 Mortality in Observational Studies of Rosiglitazone Compared to Pioglitazone:

377 Three observational studies in elderly diabetic patients (age 65 years and older) found that
378 rosiglitazone statistically significantly increased the risk of all-cause mortality compared to use
379 of pioglitazone.²⁻⁴ One observational study⁵ in patients with a mean age of 54 years found no
380 difference in all-cause mortality between patients treated with rosiglitazone compared to
381 pioglitazone and reported similar results in the subpopulation of patients >65 years of age. One
382 additional small, prospective, observational study¹⁰ found no statistically significant differences
383 for CV mortality and all-cause mortality in patients treated with rosiglitazone compared to
384 pioglitazone.

385 **5.4 Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program**

386 Because of the potential increased risk of myocardial infarction, AVANDAMET is
387 available only through a restricted distribution program called the AVANDIA-Rosiglitazone
388 Medicines Access Program [see *Indications and Usage (1)*]. Both prescribers and patients must
389 enroll in the program to be able to prescribe or receive AVANDAMET, respectively.
390 AVANDAMET will be available only from specially certified pharmacies participating in the
391 program. As part of the program, prescribers will be educated about the potential increased risk
392 of myocardial infarction and the need to limit the use of AVANDAMET to eligible patients.
393 Prescribers will need to discuss with patients the risks and benefits of taking AVANDAMET. To
394 enroll, call 1-800-AVANDIA or visit www.AVANDIA.com.

395 **5.5 Edema**

396 AVANDAMET should be used with caution in patients with edema. In a clinical trial in
397 healthy volunteers who received rosiglitazone 8 mg once daily for 8 weeks, there was a
398 statistically significant increase in median plasma volume compared to placebo. Since
399 thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or
400 lead to congestive heart failure, AVANDAMET should be used with caution in patients at risk
401 for heart failure. Patients should be monitored for signs and symptoms of heart failure [see
402 **Boxed Warning**, *Warnings and Precautions (5.2)*, and *Patient Counseling Information (17.1)*].

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

5.6 Weight Gain

Dose-related weight gain was seen with rosiglitazone alone and rosiglitazone together with other hypoglycemic agents (see Table 6). No overall change in median weight was observed with AVANDAMET in drug-naïve patients. The mechanism of weight gain with rosiglitazone is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 6. 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 + 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 + Insulin				
Duration	Control Group		AVANDAMET + Insulin	
24 weeks	Insulin	2.6 kg (0.3, 4.8) N = 145	3.3 kg (1.5, 6.0) N = 147	

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

In postmarketing experience with rosiglitazone alone or in combination with other hypoglycemic agents, there have been rare reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such

423 increases should be assessed for fluid accumulation and volume-related events such as excessive
424 edema and congestive heart failure [see **Boxed Warning**].

425 **5.7 Hepatic Effects**

426 **Metformin:** Since impaired hepatic function has been associated with some cases of
427 lactic acidosis, AVANDAMET should generally be avoided in patients with clinical or
428 laboratory evidence of hepatic disease.

429 **Rosiglitazone:** Liver enzymes should be measured prior to the initiation of therapy with
430 AVANDAMET in all patients and periodically thereafter per the clinical judgment of the
431 healthcare professional. Therapy with AVANDAMET should not be initiated in patients with
432 increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). Patients with mildly
433 elevated liver enzymes (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy
434 with AVANDAMET should be evaluated to determine the cause of the liver enzyme elevation.
435 Initiation of, or continuation of, therapy with AVANDAMET in patients with mild liver enzyme
436 elevations should proceed with caution and include close clinical follow-up, including more
437 frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen.
438 If at any time ALT levels increase to >3X the upper limit of normal in patients on therapy with
439 AVANDAMET, liver enzyme levels should be rechecked as soon as possible. If ALT levels
440 remain >3X the upper limit of normal, therapy with AVANDAMET should be discontinued.

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

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

449 **5.8 Macular Edema**

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

460 **5.9 Fractures**

461 In a 4- to 6-year comparative trial (ADOPT) of glycemic control with monotherapy in
462 drug-naïve patients recently diagnosed with type 2 diabetes mellitus, an increased incidence of

463 bone fracture was noted in female patients taking rosiglitazone. Over the 4- to 6-year period, the
464 incidence of bone fracture in females was 9.3% (60/645) for rosiglitazone versus 3.5% (21/605)
465 for glyburide and 5.1% (30/590) for metformin. This increased incidence was noted after the first
466 year of treatment and persisted during the course of the trial. The majority of the fractures in the
467 women who received rosiglitazone occurred in the upper arm, hand, and foot. These sites of
468 fracture are different from those usually associated with postmenopausal osteoporosis (e.g., hip
469 or spine). Other trials suggest that this risk may also apply to men, although the risk of fracture
470 among women appears higher than that among men. The risk of fracture should be considered in
471 the care of patients treated with rosiglitazone, and attention given to assessing and maintaining
472 bone health according to current standards of care.

473 **5.10 Hematologic Effects**

474 Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult
475 patients treated with rosiglitazone [*see Adverse Reactions (6.2)*]. The observed changes may be
476 related to the increased plasma volume observed with treatment with rosiglitazone and may be
477 dose-related. The decrease in hemoglobin was seen more frequently in combination rosiglitazone
478 and metformin therapy than in rosiglitazone therapy alone. Vitamin B₁₂ deficiency may
479 contribute to the observed reductions in hemoglobin [*see Warnings and Precautions (5.11)*].
480 Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red
481 blood cell indices) should be performed, at least on an annual basis.

482 **5.11 Vitamin B₁₂ Levels**

483 In controlled clinical trials of metformin of 29 weeks' duration, a decrease to subnormal
484 levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, was
485 observed in approximately 7% of patients. Such decrease, possibly due to interference with B₁₂
486 absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia
487 and appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂
488 supplementation. Certain individuals (those with inadequate vitamin B₁₂ or calcium intake or
489 absorption) appear to be predisposed to developing subnormal vitamin B₁₂ levels. In these
490 patients, routine serum vitamin B₁₂ measurements at 2- to 3-year intervals may be useful.
491 Vitamin B₁₂ deficiency should be excluded if megaloblastic anemia is suspected. [*See Warnings
492 and Precautions (5.10).*]

493 **5.12 Diabetes and Blood Glucose Control**

494 Periodic fasting blood glucose and HbA_{1c} measurements should be performed to monitor
495 therapeutic response.

496 When a patient stabilized on any diabetic regimen is exposed to stress such as fever,
497 trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it
498 may be necessary to withhold AVANDAMET and temporarily administer insulin.
499 AVANDAMET may be reinstated after the acute episode is resolved.

500 Hypoglycemia does not occur in patients receiving metformin alone under usual
501 circumstances of use but could occur when caloric intake is deficient, when strenuous exercise is
502 not compensated by caloric supplementation, or during concomitant use with hypoglycemic

503 agents (such as sulfonylureas or insulin) or ethanol. Elderly, debilitated or malnourished patients,
504 and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly
505 susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly
506 and in people who are taking β -adrenergic blocking drugs.

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

509 **5.13 Ovulation**

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

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

519 **6 ADVERSE REACTIONS**

520 **6.1 Clinical Trial Experience**

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

524 The incidence and types of adverse events reported in controlled, 26-week clinical trials
525 of rosiglitazone administered in combination with metformin 2,500 mg/day in comparison to
526 adverse reactions reported in association with rosiglitazone and metformin monotherapies are
527 shown in Table 7. Overall, the types of adverse reactions without regard to causality reported
528 when rosiglitazone was used in combination with metformin were similar to those reported
529 during monotherapy with rosiglitazone.

530

531 Table 7. Adverse Events (≥5% for Rosiglitazone Plus Metformin) Reported by Patients in
532 26-week Double-blind Clinical Trials of Rosiglitazone Added to Metformin Therapy

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

533

534 Reports of hypoglycemia in patients treated with rosiglitazone added to maximum
535 metformin therapy in double-blind trials were more frequent (3.0%) than in patients treated with
536 rosiglitazone (0.6%) or metformin monotherapies (1.3%) or placebo (0.2%). Overall, anemia and
537 edema were generally mild to moderate in severity and usually did not require discontinuation of
538 treatment with rosiglitazone.

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

542 Reports of anemia (7.1%) were greater in patients treated with rosiglitazone added to
543 metformin compared to monotherapy with rosiglitazone. Lower pre-treatment
544 hemoglobin/hematocrit levels in patients enrolled in the metformin and rosiglitazone
545 combination therapy clinical trials may have contributed to the higher reporting rate of anemia in
546 these trials [see Adverse Reactions (6.2)].

547 **Combination with Insulin:** The incidence of hypoglycemia (confirmed by fingerstick
548 blood glucose concentration ≤50 mg/dL) was 14% for patients on AVANDAMET plus insulin
549 compared to 10% for patients on insulin monotherapy.

550 The incidence of edema was 7% when insulin was added to AVANDAMET compared to
551 3% with insulin monotherapy. This trial excluded patients with pre-existing heart failure or new
552 or worsening edema on AVANDAMET therapy. However, in 26-week double-blind, fixed-dose
553 trials of rosiglitazone added to insulin, edema was reported with higher frequency (rosiglitazone
554 in combination with insulin, 14.7%; insulin, 5.4%) [see Warnings and Precautions (5.2)].

555 In trials in which rosiglitazone was added to insulin, rosiglitazone increased the risk of
556 congestive heart failure. The use of rosiglitazone in combination with insulin may increase the
557 risk of myocardial infarction [see *Warnings and Precautions* (5.2, 5.3)].

558 In a trial in which insulin was added to AVANDAMET, no myocardial ischemia was
559 observed in the insulin group (N = 158), and no congestive heart failure was reported in either
560 group. There was one myocardial ischemic event and one sudden death in the group receiving
561 AVANDAMET plus insulin (N = 161). [See *Warnings and Precautions* (5.2).]

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

564 A long-term, 4- to 6-year trial (ADOPT) compared the use of rosiglitazone (n = 1,456),
565 glyburide (n = 1,441), and metformin (n = 1,454) as monotherapy in patients recently diagnosed
566 with type 2 diabetes who were not previously treated with antidiabetic medication. Table 8
567 presents adverse reactions without regard to causality; rates are expressed per 100 patient-years
568 (PY) exposure to account for the differences in exposure to trial medication across the 3
569 treatment groups.

570 In ADOPT, fractures were reported in a greater number of women treated with
571 rosiglitazone (9.3%, 2.7/100 patient-years) compared to glyburide (3.5%, 1.3/100 patient-years)
572 or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who
573 received rosiglitazone were reported in the upper arm, hand, and foot. [See *Warnings and*
574 *Precautions* (5.9).] The observed incidence of fractures for male patients was similar among the
575 3 treatment groups.

576

577 **Table 8. On-Therapy Adverse Events (≥5 Events/100 Patient-Years [PY]) in Any**
578 **Treatment Group Reported in a 4- to 6-Year Clinical Trial of Rosiglitazone as**
579 **Monotherapy (ADOPT)**

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

580

581 **6.2 Laboratory Abnormalities**

582 Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a dose-related
583 fashion in adult patients treated with rosiglitazone (mean decreases in individual trials as much
584 as 1.0 gram/dL hemoglobin and as much as 3.3% hematocrit). The changes occurred primarily

585 during the first 3 months following initiation of rosiglitazone therapy or following an increase in
586 rosiglitazone dose. The time course and magnitude of decreases were similar in patients treated
587 with a combination of rosiglitazone and other hypoglycemic agents or monotherapy with
588 rosiglitazone. Pre-treatment levels of hemoglobin and hematocrit were lower in patients in
589 metformin combination trials and may have contributed to the higher reporting rate of anemia. In
590 a single trial in pediatric patients, decreases in hemoglobin and hematocrit (mean decreases of
591 0.29 g/dL and 0.95%, respectively) were reported with rosiglitazone. White blood cell counts
592 also decreased slightly in adult patients treated with rosiglitazone. Decreases in hematologic
593 parameters may be related to increased plasma volume observed with rosiglitazone treatment.

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

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

602 Serum Transaminase Levels: In pre-approval clinical trials in 4,598 patients treated
603 with rosiglitazone encompassing approximately 3,600 patient years of exposure, and in a long-
604 term 4- to 6-year trial in 1,456 patients treated with rosiglitazone (4,954 patient-years exposure),
605 there was no evidence of drug-induced hepatotoxicity.

606 In pre-approval controlled trials, 0.2% of patients treated with rosiglitazone had
607 reversible elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and
608 0.5% on active comparators. The ALT elevations in patients treated with rosiglitazone were
609 reversible. Hyperbilirubinemia was found in 0.3% of patients treated with rosiglitazone
610 compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In
611 pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic
612 failure. [See *Warnings and Precautions (5.7)*.]

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

617 **6.3 Postmarketing Experience**

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

623 In patients receiving thiazolidinedione therapy, serious adverse events with or without a
624 fatal outcome, potentially related to volume expansion (e.g., congestive heart failure, pulmonary

625 edema, and pleural effusions) have been reported [*see **Boxed Warning and Warnings and***
626 *Precautions (5.2)*].

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

630 There are postmarketing reports with rosiglitazone of rash, pruritus, urticaria,
631 angioedema, anaphylactic reaction, Stevens-Johnson syndrome, and new onset or worsening
632 diabetic macular edema with decreased visual acuity [*see **Warnings and Precautions (5.8)***].
633 (*See also GLUCOPHAGE[®] prescribing information.*)

634 **7 DRUG INTERACTIONS**

635 **7.1 Drugs Metabolized by Cytochrome P450**

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

641 **7.2 Cationic Drugs**

642 Although drug interactions for metformin with cationic drugs (e.g., amiloride, digoxin,
643 morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and
644 vancomycin) remain theoretical (except for cimetidine), careful patient monitoring and dose
645 adjustment of AVANDAMET and/or the interfering drug is recommended in patients who are
646 taking cationic medications that are excreted via the proximal renal tubular secretory system.
647 [*See **Warnings and Precautions (5.1)** and **Clinical Pharmacology (12.4)***].]

648 **7.3 Drugs That Produce Hyperglycemia**

649 When drugs that produce hyperglycemia which may lead to loss of glycemic control are
650 administered to a patient receiving AVANDAMET, the patient should be closely observed to
651 maintain adequate glycemic control. [*See **Clinical Pharmacology (12.4)***].]

652 **8 USE IN SPECIFIC POPULATIONS**

653 **8.1 Pregnancy**

654 Pregnancy Category C.

655 All pregnancies have a background risk of birth defects, loss, or other adverse outcome
656 regardless of drug exposure. This background risk is increased in pregnancies complicated by
657 hyperglycemia and may be decreased with good metabolic control. It is essential for patients
658 with diabetes or history of gestational diabetes to maintain good metabolic control before
659 conception and throughout pregnancy. Careful monitoring of glucose control is essential in such
660 patients. Most experts recommend that insulin monotherapy be used during pregnancy to
661 maintain blood glucose levels as close to normal as possible. AVANDAMET should not be used
662 during pregnancy.

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

667 Animal Studies: No animal studies have been conducted with AVANDAMET. The
668 following data are based on findings in studies performed with rosiglitazone or metformin
669 individually.

670 *Rosiglitazone:* There was no effect on implantation or the embryo with rosiglitazone
671 treatment during early pregnancy in rats, but treatment during mid-late gestation was associated
672 with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed
673 at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human
674 AUC at the maximum recommended human daily dose of the rosiglitazone component of
675 AVANDAMET, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day).
676 Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and
677 postnatal growth, with growth retardation reversible after puberty. For effects on the placenta,
678 embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in
679 rabbits. These no-effect levels are approximately 4 times human AUC at the maximum
680 recommended human daily dose of the rosiglitazone component of AVANDAMET.
681 Rosiglitazone reduced the number of uterine implantations and live offspring when juvenile
682 female rats were treated at 40 mg/kg/day from 27 days of age through to sexual maturity
683 (approximately 68 times human AUC at the maximum recommended daily dose). The no-effect
684 level was 2 mg/kg/day (approximately 4 times human AUC at the maximum recommended daily
685 dose). There was no effect on pre- or post-natal survival or growth.

686 *Metformin:* Metformin was not teratogenic in rats and rabbits at doses up to
687 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended
688 human daily dose of 2,000 mg based on body surface area comparisons for rats and rabbits,
689 respectively. Determination of fetal concentrations demonstrated a partial placental barrier to
690 metformin.

691 **8.2 Labor and Delivery**

692 The effect of AVANDAMET or its components on labor and delivery in humans is
693 unknown.

694 **8.3 Nursing Mothers**

695 No studies have been conducted with AVANDAMET. In studies performed with the
696 individual components, both rosiglitazone-related material and metformin were detectable in
697 milk from lactating rats. It is not known whether rosiglitazone or metformin is excreted in human
698 milk. Because many drugs are excreted in human milk, AVANDAMET should not be
699 administered to a nursing woman.

700 **8.4 Pediatric Use**

701 Safety and effectiveness of AVANDAMET in pediatric patients have not been
702 established. AVANDAMET and rosiglitazone are not indicated for use in pediatric patients.

703 **8.5 Geriatric Use**

704 Metformin is known to be substantially excreted by the kidney and because the risk of
705 serious adverse reactions to the drug is greater in patients with impaired renal function,
706 AVANDAMET should only be used in patients with normal renal function [*see*
707 *Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)*].
708 Because reduced renal function is associated with increasing age, AVANDAMET should be
709 used with caution in elderly patients. Care should be taken in dose selection and should be based
710 on careful and regular monitoring of renal function. Generally, elderly patients should not be
711 titrated to the maximum dose of AVANDAMET [*see Dosage and Administration (2.4) and*
712 *Warnings and Precautions (5.1)*].

713 **10 OVERDOSAGE**

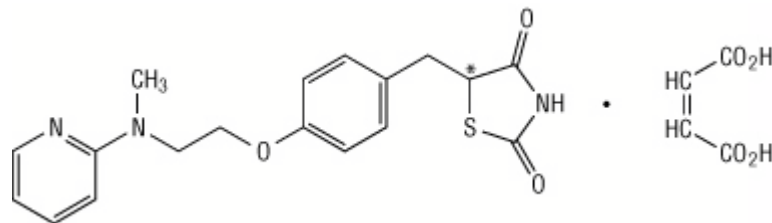
714 **Rosiglitazone:** Limited data are available with regard to overdosage in humans. In
715 clinical trials in volunteers, rosiglitazone has been administered at single oral doses of up to
716 20 mg and was well tolerated. In the event of an overdose, appropriate supportive treatment
717 should be initiated as dictated by the patient's clinical status.

718 **Metformin:** Hypoglycemia has not been seen with ingestion of up to 85 grams of
719 metformin, although lactic acidosis has occurred in such circumstances [*see Warnings and*
720 *Precautions (5.1)*]. Metformin is dialyzable with a clearance of up to 170 mL/min under good
721 hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated
722 metformin from patients in whom metformin overdosage is suspected.

723 **11 DESCRIPTION**

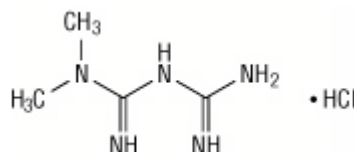
724 AVANDAMET contains 2 oral antidiabetic drugs: rosiglitazone maleate and metformin
725 hydrochloride.

726 Rosiglitazone maleate is an oral antidiabetic agent, which acts primarily by increasing
727 insulin sensitivity. Rosiglitazone improves glycemic control while reducing circulating insulin
728 levels. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the
729 biguanides, or the alpha-glucosidase inhibitors. Chemically, rosiglitazone maleate is (\pm)-5-[[4-[2-
730 (methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (Z)-2-butenedioate
731 (1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral
732 center and is present as a racemate. Due to rapid interconversion, the enantiomers are
733 functionally indistinguishable. The molecular formula is $C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$. Rosiglitazone
734 maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pK_a values
735 of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous
736 solution with pH of 2.3; solubility decreases with increasing pH in the physiological range. The
737 structural formula of rosiglitazone maleate is:



738

739 Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is
740 not chemically or pharmacologically related to any other classes of oral antidiabetic agents.
741 Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula
742 of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in
743 water and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is
744 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural
745 formula of metformin hydrochloride is:



746

747 AVANDAMET is available for oral administration as film-coated tablets containing
748 rosiglitazone maleate and metformin hydrochloride equivalent to: 2 mg rosiglitazone with
749 500 mg metformin hydrochloride (2 mg/500 mg), 4 mg rosiglitazone with 500 mg metformin
750 hydrochloride (4 mg/500 mg), 2 mg rosiglitazone with 1,000 mg metformin hydrochloride
751 (2 mg/1,000 mg), and 4 mg rosiglitazone with 1,000 mg metformin hydrochloride
752 (4 mg/1,000 mg). Inactive ingredients are: Hypromellose 2910, lactose monohydrate, magnesium
753 stearate, microcrystalline cellulose, polyethylene glycol 400, povidone 29-32, sodium starch
754 glycolate, titanium dioxide, and 1 or more of the following: Red and yellow iron oxides.

755 12 CLINICAL PHARMACOLOGY

756 12.1 Mechanism of Action

757 **AVANDAMET:** AVANDAMET combines 2 antidiabetic agents with different
758 mechanisms of action to improve glycemic control in patients with type 2 diabetes:
759 Rosiglitazone, a member of the thiazolidinedione class, and metformin, a member of the
760 biguanide class. Thiazolidinediones are insulin sensitizing agents that act primarily by enhancing
761 peripheral glucose utilization, whereas biguanides act primarily by decreasing endogenous
762 hepatic glucose production.

763 **Rosiglitazone:** Rosiglitazone improves glycemic control by improving insulin
764 sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-
765 activated receptor-gamma (PPAR γ). In humans, PPAR receptors are found in key target tissues
766 for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR γ nuclear
767 receptors regulates the transcription of insulin-responsive genes involved in the control of

768 glucose production, transport, and utilization. In addition, PPAR γ -responsive genes also
769 participate in the regulation of fatty acid metabolism.

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

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

781 **Metformin:** Metformin is an antidiabetic agent, which improves glucose tolerance in
782 patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its
783 pharmacologic mechanisms of action are different from other classes of oral antidiabetic agents.
784 Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and
785 increases peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not
786 produce hypoglycemia in either patients with type 2 diabetes or normal subjects except in special
787 circumstances [*see Warnings and Precautions (5.12)*] and does not cause hyperinsulinemia.
788 With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and
789 day-long plasma insulin response may actually decrease.

790 **12.2 Pharmacodynamics**

791 In all 26-week controlled trials, across the recommended dose range, rosiglitazone as
792 monotherapy was associated with increases in total cholesterol, LDL-cholesterol and HDL-
793 cholesterol and decreases in free fatty acids.

794 The lipid profiles of AVANDAMET as well as rosiglitazone and metformin
795 monotherapies in patients who have inadequate glycemic control on diet and exercise are shown
796 in Table 9.

797

798 Table 9. Summary of Mean^a Lipid Changes in a 32-Week Trial of AVANDAMET in
799 Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Diet
800 and Exercise

	AVANDAMET N ^b = 132	Rosiglitazone N ^b = 128	Metformin N ^b = 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%

801 ^a Data presented as geometric means throughout table.

802 ^b N = number of subjects with a baseline and end of treatment value.

803

804 The pattern of LDL, HDL, and total cholesterol changes following therapy with
805 rosiglitazone added to metformin was generally similar to those seen with rosiglitazone
806 monotherapy, and a small decrease in mean triglycerides was observed with the combination
807 therapy.

808 **12.3 Pharmacokinetics**

809 Absorption: AVANDAMET: In a bioequivalence and dose proportionality trial of
810 AVANDAMET 4 mg/500 mg, both the rosiglitazone component and the metformin component
811 were bioequivalent to coadministered 4 mg rosiglitazone tablet and 500 mg metformin tablet
812 under fasted conditions (see Table 10). In this trial, dose proportionality of rosiglitazone in the
813 combination formulations of 1 mg/500 mg and 4 mg/500 mg was demonstrated.

814

815 Table 10. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone and Metformin

		Pharmacokinetic Parameter			
Regimen	N	AUC_{0-inf} (ng.h/mL)	C_{max} (ng/mL)	T_{max}^a (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)

816 ^a Median and range presented for T_{max}.

817 Regimen A = 4 mg/500 mg AVANDAMET; Regimen B = 4 mg rosiglitazone tablet + 500 mg
818 metformin tablet; Regimen C = 1 mg/500 mg AVANDAMET

819

820 Administration of AVANDAMET 4 mg/500 mg with food resulted in no change in
821 overall exposure (AUC) for either rosiglitazone or metformin. However, there were decreases in
822 C_{max} of both components (22% for rosiglitazone and 15% for metformin, respectively) and a
823 delay in T_{max} of both components (1.5 hours for rosiglitazone and 0.5 hours for metformin,
824 respectively). These changes are not likely to be clinically significant. The pharmacokinetics of
825 both the rosiglitazone component and the metformin component of AVANDAMET when taken
826 with food were similar to the pharmacokinetics of rosiglitazone and metformin when
827 administered concomitantly as separate tablets with food.

828 **Absorption: Rosiglitazone:** The absolute bioavailability of rosiglitazone is 99%. Peak
829 plasma concentrations are observed about 1 hour after dosing. Maximum plasma concentration
830 (C_{max}) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional
831 manner over the therapeutic dose range.

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

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

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

847 Metabolism and Excretion: Rosiglitazone: Rosiglitazone is extensively metabolized
848 with no unchanged drug excreted in the urine. The major routes of metabolism were
849 N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid.
850 All the circulating metabolites are considerably less potent than parent and, therefore, are not
851 expected to contribute to the insulin-sensitizing activity of rosiglitazone. In vitro data
852 demonstrate that rosiglitazone is predominantly metabolized by Cytochrome P450 (CYP)
853 isoenzyme 2C8, with CYP2C9 contributing as a minor pathway. Following oral or intravenous
854 administration of [14 C]rosiglitazone maleate, approximately 64% and 23% of the dose was
855 eliminated in the urine and in the feces, respectively. The plasma half-life of [14 C]related
856 material ranged from 103 to 158 hours. The elimination half-life is 3 to 4 hours and is
857 independent of dose.

858 Metabolism and Excretion: Metformin: Intravenous single-dose trials in normal
859 subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo
860 hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal
861 clearance is approximately 3.5 times greater than creatinine clearance which indicates that
862 tubular secretion is the major route of metformin elimination. Following oral administration,
863 approximately 90% of the absorbed drug is eliminated via the renal route within the first
864 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the
865 elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a
866 compartment of distribution.

867 Special Populations: Renal Impairment: In subjects with decreased renal function
868 (based on measured creatinine clearance), the plasma and blood half-life of metformin is
869 prolonged and the renal clearance is decreased in proportion to the decrease in creatinine
870 clearance [see *Warnings and Precautions (5.1) and GLUCOPHAGE prescribing information*].
871 Since metformin is contraindicated in patients with renal impairment, administration of
872 AVANDAMET is contraindicated in these patients.

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

876 Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease,
877 compared to healthy subjects.

878 Therapy with AVANDAMET should not be initiated if the patient exhibits clinical
879 evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit
880 of normal) at baseline [*see Warnings and Precautions (5.7)*].

881 No pharmacokinetic trials of metformin have been conducted in subjects with hepatic
882 insufficiency.

883 **Geriatric:** Results of the population pharmacokinetics analysis (N = 716 <65 years;
884 N = 331 ≥65 years) showed that age does not significantly affect the pharmacokinetics of
885 rosiglitazone. However, limited data from controlled pharmacokinetic trials of metformin in
886 healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-
887 life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it
888 appears that the change in metformin pharmacokinetics with aging is primarily accounted for by
889 a change in renal function [*see Use in Specific Populations (8.5) and GLUCOPHAGE*
890 *prescribing information*]. Metformin treatment and therefore treatment with AVANDAMET
891 should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance
892 demonstrates that renal function is not reduced [*see Dosage and Administration (2) and*
893 *Warnings and Precautions (5.1)*].

894 **Gender:** Results of the population pharmacokinetics analysis showed that the mean oral
895 clearance of rosiglitazone in female patients (N = 405) was approximately 6% lower compared to
896 male patients of the same body weight (N = 642). In rosiglitazone and metformin combination
897 trials, efficacy was demonstrated with no gender differences in glycemic response.

898 Metformin pharmacokinetic parameters did not differ significantly between normal
899 subjects and patients with type 2 diabetes when analyzed according to gender (males = 19,
900 females = 16). Similarly, in controlled clinical trials in patients with type 2 diabetes, the
901 antihyperglycemic effect of metformin tablets was comparable in males and females.

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

905 No trials of metformin pharmacokinetic parameters according to race have been
906 performed. In controlled clinical trials of metformin in patients with type 2 diabetes, the
907 antihyperglycemic effect was comparable in whites (N = 249), blacks (N = 51), and Hispanics
908 (N = 24).

909 **Pediatric:** No pharmacokinetic data from trials in pediatric subjects are available for
910 AVANDAMET.

911 **12.4 Drug-Drug Interactions**

912 **Rosiglitazone: Drugs That Inhibit, Induce, or are Metabolized by Cytochrome**
913 **P450:** In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the
914 major P450 enzymes at clinically relevant concentrations. In vitro data demonstrate that

915 rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9. [See Drug
916 *Interactions (7.1).*]

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

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

925 **Rifampin:** Rifampin administration (600 mg once a day), an inducer of CYP2C8, for 6
926 days is reported to decrease rosiglitazone AUC by 66%, compared to the administration of
927 rosiglitazone (8 mg) alone.¹¹ [See *Drug Interactions (7.1).*]

928 **Metformin: Cationic Drugs:** Cationic drugs (e.g., amiloride, digoxin, morphine,
929 procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that
930 are eliminated by renal tubular secretion theoretically have the potential for interaction with
931 metformin by competing for common renal tubular transport systems. Such interaction between
932 metformin and oral cimetidine has been observed in normal healthy volunteers in both single-
933 and multiple-dose, metformin-cimetidine drug interaction trials, with a 60% increase in peak
934 metformin plasma and whole blood concentrations and a 40% increase in plasma and whole
935 blood metformin AUC. There was no change in elimination half-life in the single-dose trial.
936 Metformin had no effect on cimetidine pharmacokinetics. [See *Warnings and Precautions (5.1)*
937 *and Drug Interactions (7.2).*]

938 **Furosemide:** A single-dose, metformin-furosemide drug interaction trial in healthy
939 subjects demonstrated that pharmacokinetic parameters of both compounds were affected by
940 coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood
941 AUC by 15%, without any significant change in metformin renal clearance. When administered
942 with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than
943 when administered alone, and the terminal half-life was decreased by 32%, without any
944 significant change in furosemide renal clearance. No information is available about the
945 interaction of metformin and furosemide when coadministered chronically.

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

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

955 In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin
956 and ibuprofen were not affected when coadministered in single-dose interaction trials.

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

960 **13 NONCLINICAL TOXICOLOGY**

961 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

962 No animal studies have been conducted with AVANDAMET. The following data are
963 based on findings in studies performed with rosiglitazone or metformin individually.

964 Rosiglitazone: A 2-year carcinogenicity study was conducted in Charles River CD-1
965 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately
966 12 times human AUC at the maximum recommended human daily dose of the rosiglitazone
967 component of AVANDAMET). Sprague-Dawley rats were dosed for 2 years by oral gavage at
968 doses of 0.05, 0.3, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times
969 human AUC at the maximum recommended human daily dose of the rosiglitazone component of
970 AVANDAMET for male and female rats, respectively).

971 Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of
972 adipose hyperplasia in the mouse at doses ≥ 1.5 mg/kg/day (approximately 2 times human AUC
973 at the maximum recommended human daily dose of the rosiglitazone component of
974 AVANDAMET). In rats, there was a significant increase in the incidence of benign adipose
975 tissue tumors (lipomas) at doses ≥ 0.3 mg/kg/day (approximately 2 times human AUC at the
976 maximum recommended human daily dose of the rosiglitazone component of AVANDAMET).
977 These proliferative changes in both species are considered due to the persistent pharmacological
978 overstimulation of adipose tissue.

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

984 Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day
985 (approximately 116 times human AUC at the maximum recommended human daily dose of the
986 rosiglitazone component of AVANDAMET). Rosiglitazone altered estrous cyclicity
987 (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower
988 plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the
989 maximum recommended human daily dose of the rosiglitazone component of AVANDAMET,
990 respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC
991 at the maximum recommended human daily dose of the rosiglitazone component of
992 AVANDAMET). In juvenile rats dosed from 27 days of age through to sexual maturity (at up to
993 40 mg/kg/day), there was no effect on male reproductive performance, or on estrous cyclicity,

994 mating performance or pregnancy incidence in females (approximately 68 times human AUC at
995 the maximum recommended daily dose of rosiglitazone). In monkeys, rosiglitazone (0.6 and
996 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended
997 human daily dose of the rosiglitazone component of AVANDAMET, respectively) diminished
998 the follicular phase rise in serum estradiol with consequential reduction in the luteinizing
999 hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for
1000 these effects appears to be direct inhibition of ovarian steroidogenesis.

1001 **Metformin:** Long-term carcinogenicity studies have been performed in rats (dosing
1002 duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including
1003 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately 4 times
1004 the maximum recommended human daily dose of 2,000 mg of the metformin component of
1005 AVANDAMET based on body surface area comparisons. No evidence of carcinogenicity with
1006 metformin was found in either male or female mice. Similarly, there was no tumorigenic
1007 potential observed with metformin in male rats. There was, however, an increased incidence of
1008 benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

1009 There was no evidence of mutagenic potential of metformin in the following in vitro
1010 tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal
1011 aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also
1012 negative.

1013 Fertility of male or female rats was unaffected by metformin when administered at doses
1014 as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human
1015 daily dose of the metformin component of AVANDAMET based on body surface area
1016 comparisons.

1017 **13.2 Animal Toxicology**

1018 Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs
1019 (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at
1020 the maximum recommended human daily dose of the rosiglitazone component of
1021 AVANDAMET, respectively). Effects in juvenile rats were consistent with those seen in adults.
1022 Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues,
1023 which may be due to increased heart work as a result of plasma volume expansion.

1024 **14 CLINICAL STUDIES**

1025 AVANDAMET was not studied in patients previously treated with metformin
1026 monotherapy; however, the combination of rosiglitazone and metformin was compared to
1027 rosiglitazone and metformin monotherapies in clinical trials. Bioequivalence between
1028 AVANDAMET and coadministered rosiglitazone tablets and metformin tablets has been
1029 demonstrated [*see Clinical Pharmacology (12.3)*].

1030 A total of 670 patients with type 2 diabetes participated in two 26-week, randomized,
1031 double-blind, placebo/active-controlled trials designed to assess the efficacy of rosiglitazone in
1032 combination with metformin. Rosiglitazone, administered in either once-daily or twice-daily

1033 dosing regimens, was added to the therapy of patients who were inadequately controlled on
1034 2.5 grams/day of metformin.

1035 In one trial, patients inadequately controlled on 2.5 grams/day of metformin (mean
1036 baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were randomized to receive
1037 rosiglitazone 4 mg once daily, rosiglitazone 8 mg once daily, or placebo in addition to
1038 metformin. A statistically significant improvement in FPG and HbA1c was observed in patients
1039 treated with the combinations of metformin and rosiglitazone 4 mg once daily and rosiglitazone
1040 8 mg once daily, versus patients continued on metformin alone (see Table 11).

1041

1042 Table 11. Glycemic Parameters in a 26-Week Trial of Rosiglitazone Added to Metformin
1043 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 ^a	-53 ^a
% 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 ^a	-1.2 ^a
% of patients with HbA1c $\geq 0.7\%$ decrease from baseline	11%	45%	52%

1044 ^a $P < 0.0001$ compared to metformin.

1045

1046 In a second 26-week trial, patients with type 2 diabetes inadequately controlled on
1047 2.5 grams/day of metformin who were randomized to receive the combination of rosiglitazone
1048 4 mg twice daily and metformin (N = 105) showed a statistically significant improvement in
1049 glycemic control with a mean treatment effect for FPG of -56 mg/dL and a mean treatment effect
1050 for HbA1c of -0.8% over metformin alone. The combination of metformin and rosiglitazone
1051 resulted in lower levels of FPG and HbA1c than either agent alone.

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1083 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1084 Each film-coated oval tablet contains rosiglitazone as the maleate and metformin
1085 hydrochloride as follows:

- 1086 2 mg/500 mg – pale pink, tablet, debossed with gsk on one side and 2/500 on the other.
1087 4 mg/500 mg – orange, tablet, debossed with gsk on one side and 4/500 on the other.
1088 2 mg/1,000 mg – yellow, tablet, debossed with gsk on one side and 2/1000 on the other.
1089 4 mg/1,000 mg – pink, tablet, debossed with gsk on one side and 4/1000 on the other.

1090
1091 2 mg/500 mg bottles of 60: NDC 0173-0837-18

1092 4 mg/500 mg bottles of 60: NDC 0173-0839-18

1093 2 mg/1,000 mg bottles of 60: NDC 0173-0838-18

1094 4 mg/1,000 mg bottles of 60: NDC 0173-0840-18

1095

1096 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Dispense in a
1097 tight, light-resistant container.

1098 **17 PATIENT COUNSELING INFORMATION**

1099 See Medication Guide.

1100 **17.1 Patient Advice**

1101 There are multiple medications available to treat type 2 diabetes. The benefits and risks
1102 of each available diabetes medication should be taken into account when choosing a particular
1103 diabetes medication for a given patient.

1104 Patients should be informed of the risks and benefits of AVANDAMET. AVANDAMET
1105 should only be taken by adults with type 2 diabetes who are already taking rosiglitazone, or who
1106 are not already taking rosiglitazone and are unable to achieve adequate glycemic control on other
1107 diabetes medications, and, in consultation with their healthcare provider, have decided not to
1108 take pioglitazone (ACTOS) or pioglitazone-containing medications (ACTOPLUS MET,
1109 ACTOPLUS MET XR, DUETACT) for medical reasons. Inform patients that they must be
1110 enrolled in the AVANDIA-Rosiglitazone Medicines Access Program in order to receive
1111 AVANDAMET.

1112 Patients should be informed of the following:

- 1113 • The risks of lactic acidosis, its symptoms, and conditions that predispose to its development,
1114 as noted in the WARNINGS and PRECAUTIONS sections, should be explained to patients.
1115 Patients should be advised to discontinue AVANDAMET immediately and to promptly
1116 notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual
1117 somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose
1118 level of AVANDAMET, gastrointestinal symptoms, which are common during initiation of
1119 metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal
1120 symptoms could be due to lactic acidosis or other serious disease.
- 1121 • Avoid excessive alcohol intake, either acute or chronic, while receiving AVANDAMET.
- 1122 • AVANDAMET is not recommended for patients with symptomatic heart failure.
- 1123 • Results of a set of clinical trials suggest that treatment with AVANDAMET is associated
1124 with an increased risk for myocardial infarction (heart attack), especially in patients taking
1125 insulin. Clinical trials have not shown any difference between rosiglitazone and comparator
1126 medications in overall mortality or CV-related mortality.
- 1127 • AVANDAMET is not recommended for patients who are taking insulin.
- 1128 • Management of type 2 diabetes should include diet control. Caloric restriction, weight loss,
1129 and exercise are essential for the proper treatment of the diabetic patient because they help
1130 improve insulin sensitivity. This is important not only in the primary treatment of type 2
1131 diabetes but also in maintaining the efficacy of drug therapy.

- 1132 • It is important to adhere to dietary instructions and to regularly have blood glucose,
1133 glycosylated hemoglobin (HbA1c), renal function, and hematologic parameters tested. It can
1134 take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of
1135 AVANDAMET.
- 1136 • Blood will be drawn to check their liver function prior to the start of therapy and periodically
1137 thereafter per the clinical judgment of the healthcare professional. Patients with unexplained
1138 symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should
1139 immediately report these symptoms to their physician.
- 1140 • Patients who experience an unusually rapid increase in weight or edema or who develop
1141 shortness of breath or other symptoms of heart failure while on AVANDAMET should
1142 immediately report these symptoms to their physician.
- 1143 • Therapy with AVANDAMET, like other thiazolidinediones, may result in ovulation in some
1144 premenopausal anovulatory women. As a result, these patients may be at an increased risk for
1145 pregnancy while taking AVANDAMET. Thus, adequate contraception in premenopausal
1146 women should be recommended. This possible effect has not been specifically investigated
1147 in clinical trials so the frequency of this occurrence is not known.

1148

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