NDC 0093-**7322**-06

ROSIGLITAZONE MALEATE Tablets

2 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

60 TABLETS

TEVA

* Each film-coated tablet contains rosiglitazone maleate equivalent to 2 mg rosiglitazone.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 12/2012

N 3 0093-7322-06 1

Reference ID: 3248447

NDC 0093-**7323**-01

ROSIGLITAZONE MALEATE Tablets

4 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

100 TABLETS

TEVA

* Each film-coated tablet contains rosiglitazone maleate equivalent to 4 mg rosiglitazone.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

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Sellersville, PA 18960

N 3 0093-7323-01 3

Reference ID: 3248447

NDC 0093-**7323**-56

ROSIGLITAZONE MALEATE Tablets

4 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

30 TABLETS

TEVA

* Each film-coated tablet contains rosiglitazone maleate equivalent to 4 mg rosiglitazone.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

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Iss. 12/2012

N 3 0093-7323-56 3

Reference ID: 3248447

NDC 0093-**7323**-05

ROSIGLITAZONE MALEATE Tablets

4 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

500 TABLETS

TEVA

*Each film-coated tablet contains rosiglitazone maleate equivalent to 4 mg rosiglitazone.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

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N 3 0093-7323-05 1

Reference ID: 3248447

NDC 0093-**7324**-01

ROSIGLITAZONE MALEATE Tablets

8 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

100 TABLETS

TEVA

* Each film-coated tablet contains rosiglitazone maleate equivalent to 8 mg rosiglitazone.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

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N 3 0093-7324-01 0

Reference ID: 3248447

NDC 0093-**7324**-56

ROSIGLITAZONE MALEATE Tablets

8 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

30 TABLETS

TEVA

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Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

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Iss. 12/2012

N 0093-7324-05 8

Reference ID: 3248447

NDC 0093-**7322**-06

ROSIGLITAZONE MALEATE Tablets

2 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

60 TABLETS

TEVA

* Each film-coated tablet contains rosiglitazone maleate equivalent to 2 mg rosiglitazone.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

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Reference ID: 3248447

NDC 0093-**7323**-01

ROSIGLITAZONE MALEATE Tablets

4 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

100 TABLETS

TEVA

* Each film-coated tablet contains rosiglitazone maleate equivalent to 4 mg rosiglitazone.

Usual Dosage: See package insert for full prescribing information.

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ROSIGLITAZONE MALEATE Tablets

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Reference ID: 3248447

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ROSIGLITAZONE MALEATE Tablets

4 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

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TEVA

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Iss. 12/2012

N 0093-7324-05 8

Reference ID: 3248447

ROSIGLITAZONE MALEATE TABLETS

℞ only

7322
7323
7324

Iss. 8/2012

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ROSIGLITAZONE maleate tablets for oral use
Initial U.S. Approval: 1999

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION

See full prescribing information for complete boxed warning.

- **Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (5.1). After initiation of rosiglitazone maleate tablets, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone maleate tablets must be considered.**
- **Rosiglitazone maleate tablets are not recommended in patients with symptomatic heart failure. Initiation of rosiglitazone maleate tablets in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.1)**
- **A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared rosiglitazone maleate to placebo, showed rosiglitazone maleate 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 maleate 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 maleate 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. (5.2)**
- **Because of the potential increased risk of myocardial infarction, rosiglitazone maleate tablets are 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 (5.3)*].**

---- RECENT MAJOR CHANGES ----

Boxed Warning	02/2011
Indications and Usage (1)	02/2011
Dosage and Administration (2)	02/2011
Warnings and Precautions, Cardiac Failure (5.1)	02/2011
Warnings and Precautions, Major Adverse Cardiovascular Events (5.2)	02/2011
Warnings and Precautions, Rosiglitazone REMS Program (5.3)	05/2012
Warnings and Precautions, Fractures (5.8)	02/2011

----- INDICATIONS AND USAGE -----

Rosiglitazone maleate tablets are a thiazolidinedione antidiabetic agent. After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of rosiglitazone maleate tablets, this drug is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are:

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

Other Important Limitations of Use:

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

-- DOSAGE AND ADMINISTRATION --

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

- DOSAGE FORMS AND STRENGTHS -

Round, standard-convex, coated tablets in the following strengths:

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

------- CONTRAINDICATIONS -------

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

-- WARNINGS AND PRECAUTIONS --

- Fluid retention, which may exacerbate or lead to heart failure, may occur. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk of other cardiovascular effects. (5.1)
- Increased risk of myocardial infarction has been observed in a meta-analysis of 52 clinical trials (incidence rate 0.4% versus 0.3%). (5.2)
- Coadministration of rosiglitazone maleate and insulin is not recommended. (1, 5.1, 5.2)
- Dose-related edema (5.4), weight gain (5.5), and anemia (5.9) may occur.
- Macular edema has been reported. (5.7)
- Increased incidence of bone fracture. (5.8)

------ ADVERSE REACTIONS ------

Common adverse reactions (> 5%) reported in clinical trials without regard to causality were upper respiratory tract infection, injury, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TEVA USA, PHARMACOVIGILANCE at 1-888-838-2872, X6351 or drug.safety@tevapharm.com; or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

------- DRUG INTERACTIONS -------

Inhibitors of CYP2C8 (e.g., gemfibrozil) may increase rosiglitazone levels; inducers of CYP2C8 (e.g., rifampin) may decrease rosiglitazone levels. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION

- Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients [*see Warnings and Precautions (5.1)*]. After initiation of rosiglitazone maleate tablets, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone maleate tablets must be considered.
- Rosiglitazone maleate tablets are not recommended in patients with symptomatic heart failure. Initiation of rosiglitazone maleate tablets in patients with established NYHA Class III or IV heart failure is contraindicated [*see Contraindications (4) and Warnings and Precautions (5.1)*].
- A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared rosiglitazone maleate to placebo, showed rosiglitazone maleate 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 maleate 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 maleate 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 [*see Warnings and Precautions (5.2)*].
- Because of the potential increased risk of myocardial infarction, rosiglitazone maleate tablets are 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 (5.3)*].

1 INDICATIONS AND USAGE

After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of rosiglitazone maleate tablets, this drug is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are:

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

Other Important Limitations of Use:

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

2 DOSAGE AND ADMINISTRATION

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

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

The total daily dose of rosiglitazone maleate tablets should not exceed 8 mg.

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

2.1 Specific Patient Populations

__Renal Impairment:__ No dosage adjustment is necessary when rosiglitazone maleate tablets are used as monotherapy in patients with renal impairment. Since metformin is contraindicated in such patients, concomitant administration of metformin and rosiglitazone maleate tablets are also contraindicated in patients with renal impairment.

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

__Pediatric:__ Data are insufficient to recommend pediatric use of rosiglitazone maleate tablets [*see Use in Specific Populations (8.4)*].

3 DOSAGE FORMS AND STRENGTHS

Round, standard-convex, coated tablet contains rosiglitazone as the maleate as follows:

- 2 mg – pink, debossed with "93" on one side and "7322" on the other
- 4 mg – orange, debossed with "93" on one side and "7323" on the other
- 8 mg – red-brown, debossed with "93" on one side and "7324" on the other

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Failure

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

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

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

Events	Rosiglitazone Maleate	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%)

[a] Includes hospitalization for any cardiovascular reason.

Initiation of rosiglitazone maleate tablets in patients with established NYHA Class III or IV heart failure is contraindicated. Rosiglitazone maleate tablets are not recommended in patients with symptomatic heart failure [*see Boxed Warning*].

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

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

__Congestive Heart Failure During Coadministration of Rosiglitazone Maleate With Insulin:__ In trials in which rosiglitazone maleate was added to insulin, rosiglitazone maleate increased the risk of congestive heart failure. Coadministration of rosiglitazone maleate and insulin is not recommended [*see Indications and Usage (1) and Warnings and Precautions (5.2)*].

In 7 controlled, randomized, double-blind trials which had durations from 16 to 26 weeks and which were included in a meta-analysis[1] [*see Warnings and Precautions (5.2)*], patients with type 2 diabetes mellitus were randomized to coadministration of rosiglitazone maleate and insulin (N = 1,018) or insulin (N = 815). In these 7 trials, rosiglitazone maleate was added to insulin. These trials included patients with long-standing diabetes (median duration of 12 years) and a high prevalence of preexisting medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. The total number of patients with emergent congestive heart failure was 23 (2.3%) and 8 (1.0%) in the rosiglitazone maleate plus insulin and insulin groups, respectively.

__Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing Rosiglitazone Maleate to Pioglitazone (ACTOS):__ Three observational studies[2-4] in elderly diabetic patients (age 65 years and older) found that rosiglitazone maleate statistically significantly increased the risk of hospitalized heart failure compared to use of pioglitazone (ACTOS). One other observational study[5] in patients with a mean age of 54 years, which also included an analysis in a subpopulation of patients > 65 years of age, found no statistically significant increase in emergency department visits or hospitalization for heart failure in patients treated with rosiglitazone maleate compared to pioglitazone (ACTOS) in the older subgroup.

5.2 Major Adverse Cardiovascular Events

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

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

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

Event[a]	Rosiglitazone Maleate (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)

[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).

In this analysis, a statistically significant increased risk of myocardial infarction with rosiglitazone maleate 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 maleate 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 maleate 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 3**).

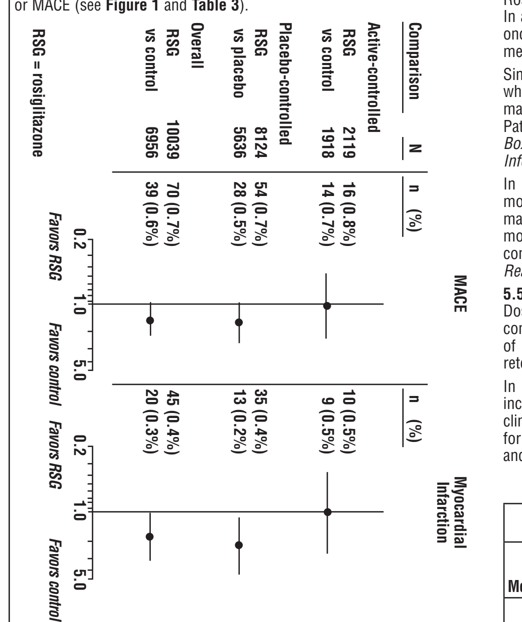

Figure 1. Forest Plot of Odds Ratios (95% Confidence Intervals) for MACE and Myocardial Infarction in the Meta-Analysis of 52 Clinical Trials

Table 3. Occurrence of MACE and Myocardial Infarction in a Meta-Analysis of 52 Clinical Trials by Trial Type

			MACE		Myocardial Infarction	
		N	n (%)	OR (95% CI)	n (%)	OR (95% CI)
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

Of the placebo-controlled trials in the meta-analysis, 7 trials had patients randomized to rosiglitazone maleate plus insulin or insulin. There were more patients in the rosiglitazone plus insulin group compared to the insulin group with myocardial infarctions, MACE, cardiovascular deaths, and all-cause deaths (see **Table 4**). The total number of patients with stroke was 5 (0.5%) and 4 (0.5%) in the rosiglitazone maleate plus insulin and insulin groups, respectively. The use of rosiglitazone maleate in combination with insulin may increase the risk of myocardial infarction.

Table 4. Occurrence of Cardiovascular Events for Rosiglitazone Maleate in Combination With Insulin in a Meta-Analysis of 52 Clinical Trials

Event[a]	Rosiglitazone Maleate (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)

ND = not defined

[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).

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

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

In a long-term, randomized, placebo-controlled, 2 x 2 factorial trial intended to evaluate rosiglitazone maleate, and separately ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on progression to overt diabetes in 5,269 subjects with glucose intolerance, the incidence of myocardial infarction was higher in the subset of subjects who received rosiglitazone maleate in combination with ramipril than among subjects who received ramipril alone but not in the subset of subjects who received rosiglitazone maleate alone compared to placebo.[6] The higher incidence of myocardial infarction among subjects who received rosiglitazone maleate in combination with ramipril was not confirmed in the two other large (total N = 8,798) long-term, randomized, active-controlled clinical trials conducted in patients with type 2 diabetes, in which 30% and 40% of patients in the two trials reported angiotensin-converting enzyme inhibitor use at baseline.[7,8]

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

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

__Mortality in Observational Studies of Rosiglitazone Maleate Compared to Pioglitazone (ACTOS):__ Three observational studies in elderly diabetic patients (age 65 years and older) found that rosiglitazone maleate statistically significantly increased the risk of all-cause mortality compared to use of pioglitazone (ACTOS).[2-4] One observational study[5] in patients with a mean age of 54 years found no difference in all-cause mortality between patients treated with rosiglitazone maleate compared to pioglitazone (ACTOS) and reported similar results in the subpopulation of patients > 65 years of age. One additional small, prospective, observational study[10] found no statistically significant differences for CV mortality and all-cause mortality in patients treated with rosiglitazone maleate compared to pioglitazone (ACTOS).

5.3 Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program

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

5.4 Edema

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

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

In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with rosiglitazone maleate, 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 maleate [*see Adverse Reactions (6.1)*].

5.5 Weight Gain

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

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

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

		Control Group		Rosiglitazone 4 mg	Rosiglitazone 8 mg
Monotherapy	Duration		Median (25th, 75th percentile)	Median (25th, 75th percentile)	Median (25th, 75th percentile)
	26 weeks	placebo	-0.9 (-2.8, 0.9) N = 210	1.0 (-0.9, 3.6) N = 436	3.1 (1.1, 5.8) N = 439
	52 weeks	sulfonylurea	2.0 (0, 4.0) N = 173	2.0 (-0.6, 4.0) N = 150	2.6 (0, 5.3) N = 157
Combination therapy					
Sulfonylurea	24 to 26 weeks	sulfonylurea	0 (-1.0, 1.3) N = 1,155	2.2 (0.5, 4.0) N = 613	3.5 (1.4, 5.9) N = 841
Metformin	26 weeks	metformin	-1.4 (-3.2, 0.2) N = 175	0.8 (-1.0, 2.6) N = 100	2.1 (0, 4.3) N = 184
Insulin	26 weeks	insulin	0.9 (-0.5, 2.7) N = 162	4.1 (1.4, 6.3) N = 164	5.4 (3.4, 7.3) N = 150
Sulfonylurea + metformin	26 weeks	sulfonylurea + metformin	0.2 (-1.2, 1.6) N = 272	2.5 (0.8, 4.6) N = 275	4.5 (2.4, 7.3) N = 276

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

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

5.6 Hepatic Effects

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

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

5.7 Macular Edema

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

5.8 Fractures

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

5.9 Hematologic Effects

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

5.10 Diabetes and Blood Glucose Control

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

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

5.11 Ovulation

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

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

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

__Adult:__ In clinical trials, approximately 9,900 patients with type 2 diabetes have been treated with rosiglitazone maleate.

Short-Term Trials of Rosiglitazone Maleate as Monotherapy and in Combination With Other Hypoglycemic Agents: The incidence and types of adverse events reported in short-term clinical trials of rosiglitazone maleate as monotherapy are shown in **Table 6**.

Table 6. Adverse Events (≥ 5% in Any Treatment Group) Reported by Patients in Short-Term[a] Double-Blind Clinical Trials With Rosiglitazone Maleate as Monotherapy

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

[a] Short-term trials ranged from 8 weeks to 1 year.
[b] Includes patients receiving glyburide (N = 514), gliclazide (N = 91), or glipizide (N = 21).

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

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

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

In clinical trials, edema was reported in 4.8% of patients receiving rosiglitazone maleate as monotherapy compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. The reporting rate of edema was higher for rosiglitazone 8 mg in sulfonylurea combinations (12.4%) compared to other combinations, with the exception of insulin. Edema was reported in 14.7% of patients receiving rosiglitazone maleate in the insulin combination trials compared to 5.4% on insulin alone. Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with rosiglitazone maleate [*see Boxed Warning and Warnings and Precautions (5.1)*]. The use of rosiglitazone maleate in combination with insulin may increase the risk of myocardial infarction [*see Warnings and Precautions (5.2)*].

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

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

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

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

	Rosiglitazone Maleate	Glyburide	Metformin
	N = 1,456 PY = 4,954	N = 1,441 PY = 4,244	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

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

6.2 Laboratory Abnormalities

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

__Lipids:__ Changes in serum lipids have been observed following treatment with rosiglitazone maleate in adults [*see Clinical Pharmacology (12.2)*]. Small changes in serum lipid parameters were reported in children treated with rosiglitazone maleate for 24 weeks.

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

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

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

6.3 Postmarketing Experience

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

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

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

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

7 DRUG INTERACTIONS

7.1 CYP2C8 Inhibitors and Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

__Pregnancy category C__

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

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

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

8.2 Labor and Delivery

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

MEDICATION GUIDE

Rosiglitazone Maleate Tablets

Read this Medication Guide carefully before you start taking rosiglitazone maleate tablets and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about rosiglitazone maleate tablets, ask your doctor or pharmacist.

What is the most important information I should know about rosiglitazone maleate tablets?

Rosiglitazone maleate tablets is available only through the AVANDIA-Rosiglitazone Medicines Access Program. Both you and your doctor must be enrolled in the program so that you can get rosiglitazone maleate tablets. To enroll, you must:

- talk to your doctor,
- understand all the risks and benefits of rosiglitazone maleate tablets, and
- agree to enroll in the program.

Rosiglitazone maleate tablets may cause serious side effects, including:
New or worse heart failure

- Rosiglitazone maleate tablets can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Heart failure means your heart does not pump blood well enough.
- If you have severe heart failure, you cannot start rosiglitazone maleate tablets.
- If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, rosiglitazone maleate tablets may not be right for you.

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

- swelling or fluid retention, especially in the ankles or legs
- shortness of breath or trouble breathing, especially when you lie down
- an unusually fast increase in weight
- unusual tiredness

Myocardial Infarction ("Heart Attack")

Rosiglitazone maleate tablets may raise the risk of a heart attack. The risk of having a heart attack may be higher in people who take rosiglitazone maleate tablets with insulin. Most people who take insulin should not also take rosiglitazone maleate tablets.

Symptoms of a heart attack can include the following:

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

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

People with diabetes have a greater risk for heart problems. It is important to work with your doctor to manage other conditions, such as high blood pressure or high cholesterol.

Rosiglitazone maleate tablets can have other serious side effects. Be sure to read the section below "**What are possible side effects of rosiglitazone maleate tablets?**"

What are rosiglitazone maleate tablets?

Rosiglitazone maleate tablets are a prescription medicine used with diet and exercise to treat certain adults with type 2 (adult-onset or non-insulin dependent) diabetes mellitus (high blood sugar) who are:

- already taking rosiglitazone maleate tablets or
- unable to control their blood sugar on other diabetes medicines, and after talking with their doctor have decided not to take pioglitazone (ACTOS®)

Rosiglitazone maleate tablets help to control high blood sugar. Rosiglitazone maleate tablets may be used alone or with other diabetes medicines. Rosiglitazone maleate tablets can help your body respond better to insulin made in your body. Rosiglitazone maleate tablets do not cause your body to make more insulin.

Rosiglitazone maleate tablets are not for people with type 1 diabetes mellitus or to treat a condition called diabetic ketoacidosis.

It is not known if rosiglitazone maleate tablets are safe and effective in children under 18 years old.

Who should not take rosiglitazone maleate tablets?

Many people with heart failure should not start taking rosiglitazone maleate tablets. See "**What should I tell my doctor before taking rosiglitazone maleate tablets?**".

What should I tell my doctor before taking rosiglitazone maleate tablets?

Before starting rosiglitazone maleate tablets, ask your doctor about what the choices are for diabetes medicines, and what the expected benefits and possible risks are for you in particular.

Before taking rosiglitazone maleate tablets, tell your doctor about all your medical conditions, including if you:

- **have heart problems or heart failure.**
- **have type 1 ("juvenile") diabetes or had diabetic ketoacidosis.** These conditions should be treated with insulin.
- **have a type of diabetic eye disease called macular edema** (swelling of the back of the eye).
- **have liver problems.** Your doctor should do blood tests to check your liver before you start taking rosiglitazone maleate tablets and during treatment as needed.
- **had liver problems while taking REZULIN® (troglitazone), another medicine for diabetes.**
- **are pregnant or plan to become pregnant.** Rosiglitazone maleate tablets should not be used during pregnancy. It is not known if rosiglitazone maleate tablets can harm your unborn baby. You and your doctor should talk about the best way to control your diabetes during pregnancy. If you are a premenopausal woman (before the "change of life") who does not have regular monthly periods, rosiglitazone maleate tablets may increase your chances of becoming pregnant. Talk to your doctor about birth control choices while taking rosiglitazone maleate tablets. Tell your doctor right away if you become pregnant while taking rosiglitazone maleate tablets.
- **are breast-feeding or planning to breast-feed.** It is not known if rosiglitazone maleate passes into breast milk. You should not use rosiglitazone maleate tablets while breast-feeding.

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

- **insulin.**
- **any medicines for high blood pressure, high cholesterol or heart failure, or for prevention of heart disease or stroke.**

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

How should I take rosiglitazone maleate tablets?

- Take rosiglitazone maleate tablets exactly as prescribed. Your doctor will tell you how many tablets to take and how often. The usual daily starting dose is 4 mg a day taken one time each day or 2 mg taken two times each day. Your doctor may need to adjust your dose until your blood sugar is better controlled.

- Rosiglitazone maleate tablets may be prescribed alone or with other diabetes medicines. This will depend on how well your blood sugar is controlled.
- Take rosiglitazone maleate tablets with or without food.
- It can take 2 weeks for rosiglitazone maleate tablets to start lowering blood sugar. It may take 2 to 3 months to see the full effect on your blood sugar level.
- If you miss a dose of rosiglitazone maleate tablets, take it as soon as you remember, unless it is time to take your next dose. Take your next dose at the usual time. Do not take double doses to make up for a missed dose.
- If you take too many rosiglitazone maleate tablets, call your doctor or poison control center right away.
- Test your blood sugar regularly as your doctor tells you.
- Diet and exercise can help your body use its blood sugar better. It is important to stay on your recommended diet, lose extra weight, and get regular exercise while taking rosiglitazone maleate tablets.
- Your doctor should do blood tests to check your liver before you start rosiglitazone maleate tablets and during treatment as needed. Your doctor should also do regular blood sugar tests (for example, "A1C") to monitor your response to rosiglitazone maleate tablets.

What are possible side effects of rosiglitazone maleate tablets?

Rosiglitazone maleate tablets may cause serious side effects including:

- **New or worse heart failure.** See "**What is the most important information I should know about rosiglitazone maleate tablets?**".
- **Heart attack.** See "**What is the most important information I should know about rosiglitazone maleate tablets?**".
- **Swelling (edema).** Rosiglitazone maleate tablets can cause swelling due to fluid retention. See "**What is the most important information I should know about rosiglitazone maleate tablets?**".
- **Weight gain.** Rosiglitazone maleate tablets can cause weight gain that may be due to fluid retention or extra body fat. Weight gain can be a serious problem for people with certain conditions including heart problems. See "**What is the most important information I should know about rosiglitazone maleate tablets?**".
- **Liver problems.** It is important for your liver to be working normally when you take rosiglitazone maleate tablets. Your doctor should do blood tests to check your liver before you start taking rosiglitazone maleate tablets and during treatment as needed. Call your doctor right away if you have unexplained symptoms such as:
  - nausea or vomiting
  - stomach pain
  - unusual or unexplained tiredness
  - loss of appetite
  - dark urine
  - yellowing of your skin or the whites of your eyes.
- **Macular edema** (a diabetic eye disease with swelling in the back of the eye). Tell your doctor right away if you have any changes in your vision. Your doctor should check your eyes regularly. Very rarely, some people have had vision changes due to swelling in the back of the eye while taking rosiglitazone maleate tablets.
- **Fractures (broken bones),** usually in the hand, upper arm or foot. Talk to your doctor for advice on how to keep your bones healthy.
- **Low red blood cell count (anemia).**
- **Low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness or hunger may mean that your blood sugar is too low. This can happen if you skip meals, if you use another medicine that lowers blood sugar, or if you have certain medical problems. Call your doctor if low blood sugar levels are a problem for you.
- **Ovulation** (release of egg from an ovary in a woman) leading to pregnancy. Ovulation may happen in premenopausal women who do not have regular monthly periods. This can increase the chance of pregnancy. See "**What should I tell my doctor before taking rosiglitazone maleate tablets?**".

The most common side effects of rosiglitazone maleate tablets reported in clinical trials included cold-like symptoms and headache.

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

How should I store rosiglitazone maleate tablets?

- Store rosiglitazone maleate tablets at room temperature, 20° to 25°C (68° to 77°F). Keep rosiglitazone maleate tablets in the container they come in.
- Safely, throw away rosiglitazone maleate tablets that are out of date or no longer needed.
- Keep rosiglitazone maleate tablets and all medicines out of the reach of children.

General information about rosiglitazone maleate tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use rosiglitazone maleate tablets for a condition for which they were not prescribed. Do not give rosiglitazone maleate tablets to other people, even if they have the same symptoms you have. They may harm them.

This Medication Guide summarizes important information about rosiglitazone maleate tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about rosiglitazone maleate tablets that is written for healthcare professionals. You can also find out more about rosiglitazone maleate tablets by calling Teva Pharmaceuticals at 1-888-838-2872, MEDICAL AFFAIRS.

What are the ingredients in rosiglitazone maleate tablets?

Active Ingredient: rosiglitazone maleate.

Inactive Ingredients: croscarmellose sodium, hypromellose (2910, 6cP), iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, titanium dioxide, and triacetin. In addition, the 2 mg tablet contains FD&C blue #2 (indigo carmine aluminum lake), the 4 mg tablet contains iron oxide black, and the 4 mg and 8 mg tablets contain iron oxide yellow.

Always check to make sure that the medicine you are taking is the correct one. Rosiglitazone maleate tablets are round and standard-convex and look like this:

2 mg – pink with "93" on one side and "7322" on the other.

4 mg – orange with "93" on one side and "7323" on the other.

8 mg – red-brown with "93" on one side and "7324" on the other.

All brand names listed are the registered trademarks of their respective owners and are not trademarks of Teva Pharmaceuticals USA.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

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8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

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

[a] Change from baseline means are least squares means adjusting for baseline HbA1c, gender, and region.

[b] Positive values for the difference favor metformin.

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

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

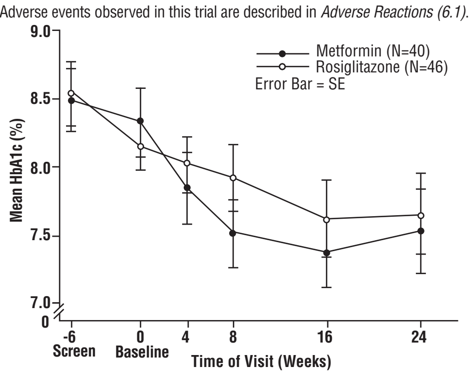


Figure 2. Mean HbA1c Over Time in a 24 Week Trial of Rosiglitazone Maleate and Metformin in Pediatric Patients — Drug-Naïve Subgroup

8.5 Geriatric Use

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

10 OVERDOSAGE

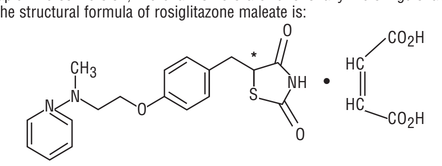
Limited data are available with regard to overdosage in humans. In clinical trials in volunteers, rosiglitazone maleate has been administered at single oral doses of up to 20 mg and was well-tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the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

11 DESCRIPTION

Rosiglitazone maleate is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. Rosiglitazone maleate improves glycemic control while reducing circulating insulin levels.

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

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



$C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$ M.W. 473.52 (357.44 free base)

Rosiglitazone maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pKa values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

Each round, standard-convex, coated tablet contains rosiglitazone maleate equivalent to rosiglitazone, 2 mg, 4 mg, or 8 mg, for oral administration. Inactive ingredients are: croscarmellose sodium, hypromellose (2910, 6cP), iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, titanium dioxide, and triacetin. In addition, the 2 mg tablet contains FD&C blue #2 (indigo carmine aluminum lake), the 4 mg tablet contains iron oxide black, and the 4 mg and 8 mg tablets contain iron oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

12.2 Pharmacodynamics

Patients with lipid abnormalities were not excluded from clinical trials of rosiglitazone maleate. In all 26 week controlled trials, across the recommended dose range, rosiglitazone maleate as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids. These changes were statistically significantly different from placebo or glyburide controls (**Table 9**).

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

The pattern of LDL and HDL changes following therapy with rosiglitazone maleate in combination with other hypoglycemic agents were generally similar to those seen with rosiglitazone maleate in monotherapy.

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

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

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

[a] Once daily and twice daily dosing groups were combined.

12.3 Pharmacokinetics

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

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

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

[a] CL/F = Oral clearance.

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

__Distribution:__ The mean (CV%) oral volume of distribution (Vss/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

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

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

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

__Population Pharmacokinetics in Patients With Type 2 Diabetes:__ Population pharmacokinetic analyses from 3 large clinical trials including 642 men and 405 women with type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume of distribution (Vss/F) were shown to increase with increases in body weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted CL/F and Vss/F values varied by < 1.7 fold and < 2.3 fold, respectively. Additionally, rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about 15%) in female patients.

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

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

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

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

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

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

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

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

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

12.4 Drug-Drug Interactions

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

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

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

__Glyburide:__ Rosiglitazone (2 mg twice daily) taken concomitantly with glyburide (3.75 to 10 mg/day) for 7 days did not alter the mean steady-state 24 hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy. Repeat doses of rosiglitazone (8 mg once daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and C_{max} of approximately 30%. In Japanese subjects, glyburide AUC and C_{max} slightly increased following coadministration of rosiglitazone maleate.

__Glimepiride:__ Single oral doses of glimepiride in 14 healthy adult subjects had no clinically significant effect on the steady-state pharmacokinetics of rosiglitazone maleate. No clinically significant reductions in glimepiride AUC and C_{max} were observed after repeat doses of rosiglitazone (8 mg once daily) for 8 days in healthy adult subjects.

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

__Acarbose:__ Coadministration of acarbose (100 mg three times daily) for 7 days in healthy volunteers had no clinically relevant effect on the pharmacokinetics of a single oral dose of rosiglitazone maleate.

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

__Warfarin:__ Repeat dosing with rosiglitazone maleate had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers.

__Ethanol:__ A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in type 2 diabetes mellitus patients treated with rosiglitazone maleate.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Monotherapy

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

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

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

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

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

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

[a] $P < 0.0001$ compared to placebo.

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

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

The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a statistically significant improvement in glycemic control from baseline (**Figure 3** and **Figure 4**). At the end of week 52, the reduction from baseline in FPG and HbA1c was -40.8 mg/dL and -0.53% with rosiglitazone 4 mg twice daily; -25.4 mg/dL and -0.27% with rosiglitazone 2 mg twice daily; and -30.0 mg/dL and -0.72% with glyburide. For HbA1c, the difference between rosiglitazone 4 mg twice daily and glyburide was not statistically significant at week 52. The initial fall in FPG with glyburide was greater than with rosiglitazone maleate; however, this effect was less durable over time. The improvement in glycemic control seen with rosiglitazone 4 mg twice daily at week 26 was maintained through week 52 of the trial.

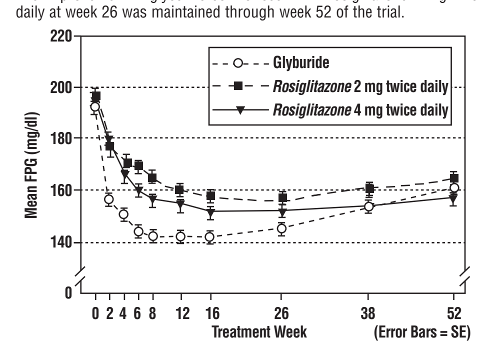


Figure 3. Mean FPG Over Time in a 52 Week Glyburide-Controlled Trial

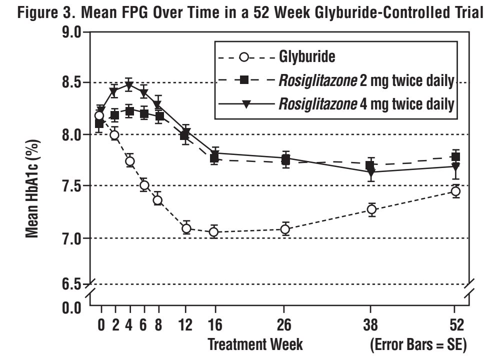


Figure 4. Mean HbA1c Over Time in a 52 Week Glyburide-Controlled Trial

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

A Diabetes Outcome Progression Trial (ADOPT) was a multicenter, double-blind, controlled trial (N = 4,351) conducted over 4 to 6 years to compare the safety and efficacy of rosiglitazone maleate, metformin, and glyburide monotherapy in patients recently diagnosed with type 2 diabetes mellitus (≤ 3 years) inadequately controlled with diet and exercise. The mean age of patients in this trial was 57 years and the majority of patients (83%) had no known history of cardiovascular disease. The mean baseline FPG and HbA1c were 152 mg/dL and 7.4%, respectively. Patients were randomized to receive either rosiglitazone 4 mg once daily, glyburide 2.5 mg once daily, or metformin 500 mg once daily, and doses were titrated to optimal glycemic control up to a maximum of 4 mg twice daily for rosiglitazone, 7.5 mg twice daily for glyburide, and 1,000 mg twice daily for metformin. The primary efficacy outcome was time to consecutive FPG > 180 mg/dL after at least 6 weeks of treatment at the maximum tolerated dose of study medication or time to inadequate glycemic control, as determined by an independent adjudication committee.

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

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

14.2 Combination With Metformin or Sulfonylurea

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

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

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

Table 12. Glycemic Parameters in a 26 Week Combination Trial of Rosiglitazone Maleate Plus Metformin

	Metformin	Rosiglitazone 4 mg once daily + metformin	Rosiglitazone 8 mg once daily + metformin
	N = 113	N = 116	N = 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 ≥ 0.7% decrease from baseline	11%	45%	52%

[a] $P < 0.0001$ compared to metformin.

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

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

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

In these trials, the combination of rosiglitazone 4 mg or 8 mg daily (administered as single or twice daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c compared to placebo plus sulfonylurea or further up-titration of the sulfonylurea. **Table 13** shows pooled data for 8 trials in which rosiglitazone maleate added to sulfonylurea was compared to placebo plus sulfonylurea.

Table 13. Glycemic Parameters in 24 to 26 Week Combination Trials of Rosiglitazone Maleate Plus Sulfonylurea

Twice Daily Divided Dosing (5 Studies)	Sulfonylurea	Rosiglitazone 2 mg twice daily + sulfonylurea	Sulfonylurea	Rosiglitazone 4 mg twice daily + sulfonylurea
	N = 397	N = 497	N = 248	N = 346
FPG (mg/dL)				
Baseline (mean)	204	198	188	187
Change from baseline (mean)	11	-29	8	-43
Difference from sulfonylurea alone (adjusted mean)	–	-42[a]	–	-53[a]
% of patients with ≥ 30 mg/dL decrease from baseline	17%	49%	15%	61%
HbA1c (%)				
Baseline (mean)	9.4	9.5	9.3	9.6
Change from baseline (mean)	0.2	-1.0	0.0	-1.6
Difference from sulfonylurea alone (adjusted mean)	–	-1.1[a]	–	-1.4[a]
% of patients with ≥ 0.7% decrease from baseline	21%	60%	23%	75%
Once Daily Dosing (3 Trials)	**Sulfonylurea**	**Rosiglitazone 4 mg once daily + sulfonylurea**	**Sulfonylurea**	**Rosiglitazone 8 mg once daily + sulfonylurea**
	N = 172	N = 172	N = 173	N = 176
FPG (mg/dL)				
Baseline (mean)	198	206	188	192
Change from baseline (mean)	17	-25	17	-43
Difference from sulfonylurea alone (adjusted mean)	–	-47[a]	–	-66[a]
% of patients with ≥ 30 mg/dL decrease from baseline	17%	48%	19%	55%
HbA1c (%)				
Baseline (mean)	8.6	8.8	8.9	8.9
Change from baseline (mean)	0.4	-0.5	0.1	-1.2
Difference from sulfonylurea alone (adjusted mean)	–	-0.9[a]	–	-1.4[a]
% of patients with ≥ 0.7% decrease from baseline	11%	36%	20%	68%

[a] $P < 0.0001$ compared to sulfonylurea alone.

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

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

14.3 Combination With Sulfonylurea Plus Metformin

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

Table 14. Glycemic Parameters in a 26 Week Combination Trial of Rosiglitazone Maleate Plus Sulfonylurea and Metformin

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

[a] $P < 0.0001$ compared to placebo.

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16 HOW SUPPLIED/STORAGE AND HANDLING

Each round, standard-convex, coated tablet contains rosiglitazone as the maleate as follows:

2 mg – pink tablets, debossed with the number "93" on one side and "7322" on the other. They are available in bottles of 60.

4 mg – orange tablets, debossed with the number "93" on one side and "7323" on the other. They are available in bottles of 30, 100, and 500.

8 mg – red-brown tablets, debossed with the number "93" on one side and "7324" on the other. They are available in bottles of 30, 100, and 500.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

17 PATIENT COUNSELING INFORMATION

See Medication Guide.

17.1 Patient Advice

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

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

Patients should be informed of the following:

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

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Iss. 8/2012

ROSIGLITAZONE MALEATE TABLETS

℞ only

7322
7323
7324

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use rosiglitazone maleate tablets safely and effectively. See full prescribing information for rosiglitazone maleate tablets.

ROSIGLITAZONE maleate tablets for oral use
Initial U.S. Approval: 1999

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION

See full prescribing information for complete boxed warning.

- **Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (5.1). After initiation of rosiglitazone maleate tablets, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone maleate tablets must be considered.**
- **Rosiglitazone maleate tablets are not recommended in patients with symptomatic heart failure. Initiation of rosiglitazone maleate tablets in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.1)**
- **A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared rosiglitazone maleate to placebo, showed rosiglitazone maleate 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 maleate 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 maleate 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. (5.2)**
- **Because of the potential increased risk of myocardial infarction, rosiglitazone maleate tablets are 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 (5.3)*].**

---- RECENT MAJOR CHANGES ----

Boxed Warning	02/2011
Indications and Usage (1)	02/2011
Dosage and Administration (2)	02/2011
Warnings and Precautions, Cardiac Failure (5.1)	02/2011
Warnings and Precautions, Major Adverse Cardiovascular Events (5.2)	02/2011
Warnings and Precautions, Rosiglitazone REMS Program (5.3)	05/2012
Warnings and Precautions, Fractures (5.8)	02/2011

----- INDICATIONS AND USAGE -----
Rosiglitazone maleate tablets are a thiazolidinedione antidiabetic agent. After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of rosiglitazone maleate tablets, this drug is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are:

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

Other Important Limitations of Use:

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

-- DOSAGE AND ADMINISTRATION --

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

- DOSAGE FORMS AND STRENGTHS -
Round, standard-convex, coated tablets in the following strengths:

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

------- CONTRAINDICATIONS -------
Initiation of rosiglitazone maleate tablets in patients with established NYHA Class III or IV heart failure is contraindicated. (4)

-- WARNINGS AND PRECAUTIONS --

- Fluid retention, which may exacerbate or lead to heart failure, may occur. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk of other cardiovascular effects. (5.1)
- Increased risk of myocardial infarction has been observed in a meta-analysis of 52 clinical trials (incidence rate 0.4% versus 0.3%). (5.2)
- Coadministration of rosiglitazone maleate and insulin is not recommended. (1, 5.1, 5.2)
- Dose-related edema (5.4), weight gain (5.5), and anemia (5.9) may occur.
- Macular edema has been reported. (5.7)
- Increased incidence of bone fracture. (5.8)

------ ADVERSE REACTIONS ------
Common adverse reactions (> 5%) reported in clinical trials without regard to causality were upper respiratory tract infection, injury, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TEVA USA, PHARMACOVIGILANCE at 1-888-838-2872, X6351 or drug.safety@tevapharm.com; or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

------- DRUG INTERACTIONS -------
Inhibitors of CYP2C8 (e.g., gemfibrozil) may increase rosiglitazone levels; inducers of CYP2C8 (e.g., rifampin) may decrease rosiglitazone levels. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL INFARCTION

- Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients [*see Warnings and Precautions (5.1)*]. After initiation of rosiglitazone maleate tablets, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone maleate tablets must be considered.
- Rosiglitazone maleate tablets are not recommended in patients with symptomatic heart failure. Initiation of rosiglitazone maleate tablets in patients with established NYHA Class III or IV heart failure is contraindicated [*see Contraindications (4) and Warnings and Precautions (5.1)*].
- A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared rosiglitazone maleate to placebo, showed rosiglitazone maleate 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 maleate 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 maleate 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 [*see Warnings and Precautions (5.2)*].
- Because of the potential increased risk of myocardial infarction, rosiglitazone maleate tablets are 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 (5.3)*].

1 INDICATIONS AND USAGE

After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of rosiglitazone maleate tablets, this drug is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are:

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

Other Important Limitations of Use:

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

2 DOSAGE AND ADMINISTRATION

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

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

The total daily dose of rosiglitazone maleate tablets should not exceed 8 mg.

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

2.1 Specific Patient Populations

__Renal Impairment:__ No dosage adjustment is necessary when rosiglitazone maleate tablets are used as monotherapy in patients with renal impairment. Since metformin is contraindicated in such patients, concomitant administration of metformin and rosiglitazone maleate tablets are also contraindicated in patients with renal impairment.

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

__Pediatric:__ Data are insufficient to recommend pediatric use of rosiglitazone maleate tablets [*see Use in Specific Populations (8.4)*].

3 DOSAGE FORMS AND STRENGTHS

Round, standard-convex, coated tablet contains rosiglitazone as the maleate as follows:

- 2 mg – pink, debossed with "93" on one side and "7322" on the other
- 4 mg – orange, debossed with "93" on one side and "7323" on the other
- 8 mg – red-brown, debossed with "93" on one side and "7324" on the other

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Failure

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

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

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

Events	Rosiglitazone Maleate	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%)

[a] Includes hospitalization for any cardiovascular reason.

Initiation of rosiglitazone maleate tablets in patients with established NYHA Class III or IV heart failure is contraindicated. Rosiglitazone maleate tablets are not recommended in patients with symptomatic heart failure [*see Boxed Warning*].

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

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

__Congestive Heart Failure During Coadministration of Rosiglitazone Maleate With Insulin:__ In trials in which rosiglitazone maleate was added to insulin, rosiglitazone maleate increased the risk of congestive heart failure. Coadministration of rosiglitazone maleate and insulin is not recommended [*see Indications and Usage (1) and Warnings and Precautions (5.2)*].

In 7 controlled, randomized, double-blind trials which had durations from 16 to 26 weeks and which were included in a meta-analysis[1] [*see Warnings and Precautions (5.2)*], patients with type 2 diabetes mellitus were randomized to coadministration of rosiglitazone maleate and insulin (N = 1,018) or insulin (N = 815). In these 7 trials, rosiglitazone maleate was added to insulin. These trials included patients with long-standing diabetes (median duration of 12 years) and a high prevalence of preexisting medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. The total number of patients with emergent congestive heart failure was 23 (2.3%) and 8 (1.0%) in the rosiglitazone maleate plus insulin and insulin groups, respectively.

__Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing Rosiglitazone Maleate to ACTOS:__ Three observational studies[2-4] in elderly diabetic patients (age 65 years and older) found that rosiglitazone maleate statistically significantly increased the risk of hospitalized heart failure compared to use of (ACTOS). One other observational study[5] in patients with a mean age of 54 years, which also included an analysis in a subpopulation of patients > 65 years of age, found no statistically significant increase in emergency department visits or hospitalization for heart failure in patients treated with rosiglitazone maleate compared to ACTOS in the older subgroup.

5.2 Major Adverse Cardiovascular Events

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

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

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

Event[a]	Rosiglitazone Maleate (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)

[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).

In this analysis, a statistically significant increased risk of myocardial infarction with rosiglitazone maleate 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 maleate 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 maleate 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 3**).

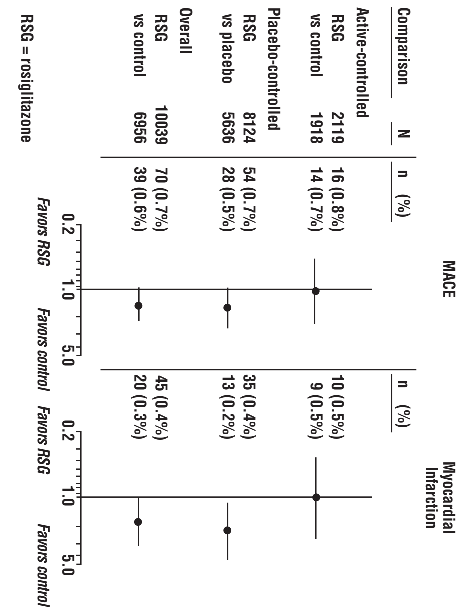

Figure 1. Forest Plot of Odds Ratios (95% Confidence Intervals) for MACE and Myocardial Infarction in the Meta-Analysis of 52 Clinical Trials

Table 3. Occurrence of MACE and Myocardial Infarction in a Meta-Analysis of 52 Clinical Trials by Trial Type

			MACE		Myocardial Infarction	
		N	n (%)	OR (95% CI)	n (%)	OR (95% CI)
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

Of the placebo-controlled trials in the meta-analysis, 7 trials had patients randomized to rosiglitazone maleate plus insulin or insulin. There were more patients in the rosiglitazone plus insulin group compared to the insulin group with myocardial infarctions, MACE, cardiovascular deaths, and all-cause deaths (see **Table 4**). The total number of patients with stroke was 5 (0.5%) and 4 (0.5%) in the rosiglitazone maleate plus insulin and insulin groups, respectively. The use of rosiglitazone maleate in combination with insulin may increase the risk of myocardial infarction.

Table 4. Occurrence of Cardiovascular Events for Rosiglitazone Maleate in Combination With Insulin in a Meta-Analysis of 52 Clinical Trials

Event[a]	Rosiglitazone Maleate (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)

ND = not defined

[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).

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

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

In a long-term, randomized, placebo-controlled, 2 x 2 factorial trial intended to evaluate rosiglitazone maleate, and separately ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on progression to overt diabetes in 5,269 subjects with glucose intolerance, the incidence of myocardial infarction was higher in the subset of subjects who received rosiglitazone maleate in combination with ramipril than among subjects who received ramipril alone but not in the subset of subjects who received rosiglitazone maleate alone compared to placebo.[6] The higher incidence of myocardial infarction among subjects who received rosiglitazone maleate in combination with ramipril was not confirmed in the two other large (total N = 8,798) long-term, randomized, active-controlled clinical trials conducted in patients with type 2 diabetes, in which 30% and 40% of patients in the two trials reported angiotensin-converting enzyme inhibitor use at baseline.[7,8]

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

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

__Mortality in Observational Studies of Rosiglitazone Maleate Compared to ACTOS:__ Three observational studies in elderly diabetic patients (age 65 years and older) found that rosiglitazone maleate statistically significantly increased the risk of all-cause mortality compared to use of ACTOS.[2-4] One observational study[5] in patients with a mean age of 54 years found no difference in all-cause mortality between patients treated with rosiglitazone maleate compared to ACTOS and reported similar results in the subpopulation of patients > 65 years of age. One additional small, prospective, observational study[10] found no statistically significant differences for CV mortality and all-cause mortality in patients treated with rosiglitazone maleate compared to ACTOS.

5.3 Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program

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

5.4 Edema

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

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

In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with rosiglitazone maleate, 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 maleate [*see Adverse Reactions (6.1)*].

5.5 Weight Gain

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

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

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

		Control Group		Rosiglitazone 4 mg	Rosiglitazone 8 mg
Monotherapy	**Duration**		**Median (25th, 75th percentile)**	**Median (25th, 75th percentile)**	**Median (25th, 75th percentile)**
	26 weeks	placebo	-0.9 (-2.8, 0.9) N = 210	1.0 (-0.9, 3.6) N = 436	3.1 (1.1, 5.8) N = 439
	52 weeks	sulfonylurea	2.0 (0, 4.0) N = 173	2.0 (-0.6, 4.0) N = 150	2.6 (0, 5.3) N = 157
Combination therapy					
Sulfonylurea	24 to 26 weeks	sulfonylurea	0 (-1.0, 1.3) N = 1,155	2.2 (0.5, 4.0) N = 613	3.5 (1.4, 5.9) N = 841
Metformin	26 weeks	metformin	-1.4 (-3.2, 0.2) N = 175	0.8 (-1.0, 2.6) N = 100	2.1 (0, 4.3) N = 184
Insulin	26 weeks	insulin	0.9 (-0.5, 2.7) N = 162	4.1 (1.4, 6.3) N = 164	5.4 (3.4, 7.3) N = 150
Sulfonylurea + metformin	26 weeks	sulfonylurea + metformin	0.2 (-1.2, 1.6) N = 272	2.5 (0.8, 4.6) N = 275	4.5 (2.4, 7.3) N = 276

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

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

5.6 Hepatic Effects

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

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

5.7 Macular Edema

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

5.8 Fractures

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

5.9 Hematologic Effects

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

5.10 Diabetes and Blood Glucose Control

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

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

5.11 Ovulation

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

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

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

__Adult:__ In clinical trials, approximately 9,900 patients with type 2 diabetes have been treated with rosiglitazone maleate.

Short-Term Trials of Rosiglitazone Maleate as Monotherapy and in Combination With Other Hypoglycemic Agents: The incidence and types of adverse events reported in short-term clinical trials of rosiglitazone maleate as monotherapy are shown in **Table 6**.

Table 6. Adverse Events (≥ 5% in Any Treatment Group) Reported by Patients in Short-Term[a] Double-Blind Clinical Trials With Rosiglitazone Maleate as Monotherapy

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

[a] Short-term trials ranged from 8 weeks to 1 year.
[b] Includes patients receiving glyburide (N = 514), gliclazide (N = 91), or glipizide (N = 21).

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

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

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

In clinical trials, edema was reported in 4.8% of patients receiving rosiglitazone maleate as monotherapy compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. The reporting rate of edema was higher for rosiglitazone 8 mg in sulfonylurea combinations (12.4%) compared to other combinations, with the exception of insulin. Edema was reported in 14.7% of patients receiving rosiglitazone maleate in the insulin combination trials compared to 5.4% on insulin alone. Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with rosiglitazone maleate [*see Boxed Warning and Warnings and Precautions (5.1)*]. The use of rosiglitazone maleate in combination with insulin may increase the risk of myocardial infarction [*see Warnings and Precautions (5.2)*].

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

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

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

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

	Rosiglitazone Maleate	Glyburide	Metformin
	N = 1,456 PY = 4,954	N = 1,441 PY = 4,244	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

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

6.2 Laboratory Abnormalities

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

__Lipids:__ Changes in serum lipids have been observed following treatment with rosiglitazone maleate in adults [*see Clinical Pharmacology (12.2)*]. Small changes in serum lipid parameters were reported in children treated with rosiglitazone maleate for 24 weeks.

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

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

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

6.3 Postmarketing Experience

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

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

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

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

7 DRUG INTERACTIONS

7.1 CYP2C8 Inhibitors and Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects
Pregnancy category C

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

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

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

8.2 Labor and Delivery

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

MEDICATION GUIDE
Rosiglitazone Maleate Tablets

Read this Medication Guide carefully before you start taking rosiglitazone maleate tablets and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about rosiglitazone maleate tablets, ask your doctor or pharmacist.

What is the most important information I should know about rosiglitazone maleate tablets?

Rosiglitazone maleate tablets is available only through the AVANDIA-Rosiglitazone Medicines Access Program. Both you and your doctor must be enrolled in the program so that you can get rosiglitazone maleate tablets. To enroll, you must:

- talk to your doctor,
- understand all the risks and benefits of rosiglitazone maleate tablets, and
- agree to enroll in the program.

Rosiglitazone maleate tablets may cause serious side effects, including:
New or worse heart failure

- Rosiglitazone maleate tablets can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Heart failure means your heart does not pump blood well enough.
- If you have severe heart failure, you cannot start rosiglitazone maleate tablets.
- If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, rosiglitazone maleate tablets may not be right for you.

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

- swelling or fluid retention, especially in the ankles or legs
- shortness of breath or trouble breathing, especially when you lie down
- an unusually fast increase in weight
- unusual tiredness

Myocardial Infarction ("Heart Attack")

Rosiglitazone maleate tablets may raise the risk of a heart attack. The risk of having a heart attack may be higher in people who take rosiglitazone maleate tablets with insulin. Most people who take insulin should not also take rosiglitazone maleate tablets.

Symptoms of a heart attack can include the following:

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

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

People with diabetes have a greater risk for heart problems. It is important to work with your doctor to manage other conditions, such as high blood pressure or high cholesterol.

Rosiglitazone maleate tablets can have other serious side effects. Be sure to read the section below "**What are possible side effects of rosiglitazone maleate tablets?**"

What are rosiglitazone maleate tablets?

Rosiglitazone maleate tablets are a prescription medicine used with diet and exercise to treat certain adults with type 2 (adult-onset or non-insulin dependent) diabetes mellitus (high blood sugar) who are:

- already taking rosiglitazone maleate tablets or
- unable to control their blood sugar on other diabetes medicines, and after talking with their doctor have decided not to take pioglitazone (ACTOS®)

Rosiglitazone maleate tablets help to control high blood sugar. Rosiglitazone maleate tablets may be used alone or with other diabetes medicines. Rosiglitazone maleate tablets can help your body respond better to insulin made in your body. Rosiglitazone maleate tablets do not cause your body to make more insulin.

Rosiglitazone maleate tablets are not for people with type 1 diabetes mellitus or to treat a condition called diabetic ketoacidosis.

It is not known if rosiglitazone maleate tablets are safe and effective in children under 18 years old.

Who should not take rosiglitazone maleate tablets?

Many people with heart failure should not start taking rosiglitazone maleate tablets. See "**What should I tell my doctor before taking rosiglitazone maleate tablets?**".

What should I tell my doctor before taking rosiglitazone maleate tablets?

Before starting rosiglitazone maleate tablets, ask your doctor about what the choices are for diabetes medicines, and what the expected benefits and possible risks are for you in particular.

Before taking rosiglitazone maleate tablets, tell your doctor about all your medical conditions, including if you:

- **have heart problems or heart failure.**
- **have type 1 ("juvenile") diabetes or had diabetic ketoacidosis.** These conditions should be treated with insulin.
- **have a type of diabetic eye disease called macular edema** (swelling of the back of the eye).
- **have liver problems.** Your doctor should do blood tests to check your liver before you start taking rosiglitazone maleate tablets and during treatment as needed.
- **had liver problems while taking REZULIN® (troglitazone), another medicine for diabetes.**
- **are pregnant or plan to become pregnant.** Rosiglitazone maleate tablets should not be used during pregnancy. It is not known if rosiglitazone maleate tablets can harm your unborn baby. You and your doctor should talk about the best way to control your diabetes during pregnancy. If you are a premenopausal woman (before the "change of life") who does not have regular monthly periods, rosiglitazone maleate tablets may increase your chances of becoming pregnant. Talk to your doctor about birth control choices while taking rosiglitazone maleate tablets. Tell your doctor right away if you become pregnant while taking rosiglitazone maleate tablets.
- **are breast-feeding or planning to breast-feed.** It is not known if rosiglitazone maleate passes into breast milk. You should not use rosiglitazone maleate tablets while breast-feeding.

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

- **insulin.**
- **any medicines for high blood pressure, high cholesterol or heart failure, or for prevention of heart disease or stroke.**

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

How should I take rosiglitazone maleate tablets?

- Take rosiglitazone maleate tablets exactly as prescribed. Your doctor will tell you how many tablets to take and how often. The usual daily starting dose is 4 mg a day taken one time each day or 2 mg taken two times each day. Your doctor may need to adjust your dose until your blood sugar is better controlled.

- Rosiglitazone maleate tablets may be prescribed alone or with other diabetes medicines. This will depend on how well your blood sugar is controlled.
- Take rosiglitazone maleate tablets with or without food.
- It can take 2 weeks for rosiglitazone maleate tablets to start lowering blood sugar. It may take 2 to 3 months to see the full effect on your blood sugar level.
- If you miss a dose of rosiglitazone maleate tablets, take it as soon as you remember, unless it is time to take your next dose. Take your next dose at the usual time. Do not take double doses to make up for a missed dose.
- If you take too many rosiglitazone maleate tablets, call your doctor or poison control center right away.
- Test your blood sugar regularly as your doctor tells you.
- Diet and exercise can help your body use its blood sugar better. It is important to stay on your recommended diet, lose extra weight, and get regular exercise while taking rosiglitazone maleate tablets.
- Your doctor should do blood tests to check your liver before you start rosiglitazone maleate tablets and during treatment as needed. Your doctor should also do regular blood sugar tests (for example, "A1C") to monitor your response to rosiglitazone maleate tablets.

What are possible side effects of rosiglitazone maleate tablets?

Rosiglitazone maleate tablets may cause serious side effects including:

- **New or worse heart failure.** See "**What is the most important information I should know about rosiglitazone maleate tablets?**".
- **Heart attack.** See "**What is the most important information I should know about rosiglitazone maleate tablets?**".
- **Swelling (edema).** Rosiglitazone maleate tablets can cause swelling due to fluid retention. See "**What is the most important information I should know about rosiglitazone maleate tablets?**".
- **Weight gain.** Rosiglitazone maleate tablets can cause weight gain that may be due to fluid retention or extra body fat. Weight gain can be a serious problem for people with certain conditions including heart problems. See "**What is the most important information I should know about rosiglitazone maleate tablets?**".
- **Liver problems.** It is important for your liver to be working normally when you take rosiglitazone maleate tablets. Your doctor should do blood tests to check your liver before you start taking rosiglitazone maleate tablets and during treatment as needed. Call your doctor right away if you have unexplained symptoms such as:
  - nausea or vomiting
  - stomach pain
  - unusual or unexplained tiredness
  - loss of appetite
  - dark urine
  - yellowing of your skin or the whites of your eyes.
- **Macular edema** (a diabetic eye disease with swelling in the back of the eye). Tell your doctor right away if you have any changes in your vision. Your doctor should check your eyes regularly. Very rarely, some people have had vision changes due to swelling in the back of the eye while taking rosiglitazone maleate tablets.
- **Fractures (broken bones),** usually in the hand, upper arm or foot. Talk to your doctor for advice on how to keep your bones healthy.
- **Low red blood cell count (anemia).**
- **Low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness or hunger may mean that your blood sugar is too low. This can happen if you skip meals, if you use another medicine that lowers blood sugar, or if you have certain medical problems. Call your doctor if low blood sugar levels are a problem for you.

Reference ID: 3248447

- **Ovulation** (release of egg from an ovary in a woman) leading to pregnancy. Ovulation may happen in premenopausal women who do not have regular monthly periods. This can increase the chance of pregnancy. See "**What should I tell my doctor before taking rosiglitazone maleate tablets?**".

The most common side effects of rosiglitazone maleate tablets reported in clinical trials included cold-like symptoms and headache.

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

How should I store rosiglitazone maleate tablets?

- Store rosiglitazone maleate tablets at room temperature, 20° to 25°C (68° to 77°F). Keep rosiglitazone maleate tablets in the container they come in.
- Safely, throw away rosiglitazone maleate tablets that are out of date or no longer needed.
- Keep rosiglitazone maleate tablets and all medicines out of the reach of children.

General information about rosiglitazone maleate tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use rosiglitazone maleate tablets for a condition for which they were not prescribed. Do not give rosiglitazone maleate tablets to other people, even if they have the same symptoms you have. They may harm them.

This Medication Guide summarizes important information about rosiglitazone maleate tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about rosiglitazone maleate tablets that is written for healthcare professionals. You can also find out more about rosiglitazone maleate tablets by calling Teva Pharmaceuticals at 1-888-838-2872, MEDICAL AFFAIRS.

What are the ingredients in rosiglitazone maleate tablets?

Active Ingredient: rosiglitazone maleate.

Inactive Ingredients: croscarmellose sodium, hypromellose (2910, 6cP), iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, titanium dioxide, and triacetin. In addition, the 2 mg tablet contains FD&C blue #2 (indigo carmine aluminum lake), the 4 mg tablet contains iron oxide black, and the 4 mg and 8 mg tablets contain iron oxide yellow.

Always check to make sure that the medicine you are taking is the correct one. Rosiglitazone maleate tablets are round and standard-convex and look like this:

2 mg – pink with "93" on one side and "7322" on the other.

4 mg – orange with "93" on one side and "7323" on the other.

8 mg – red-brown with "93" on one side and "7324" on the other.

All brand names listed are the registered trademarks of their respective owners and are not trademarks of Teva Pharmaceuticals USA.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

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8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

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

[a] Change from baseline means are least squares means adjusting for baseline HbA1c, gender, and region.

[b] Positive values for the difference favor metformin.

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

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

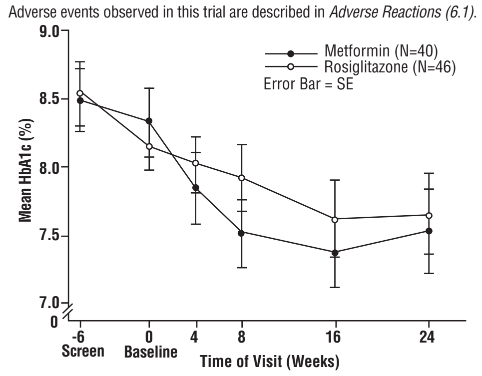


Figure 2. Mean HbA1c Over Time in a 24 Week Trial of Rosiglitazone Maleate and Metformin in Pediatric Patients — Drug-Naïve Subgroup

8.5 Geriatric Use

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

10 OVERDOSAGE

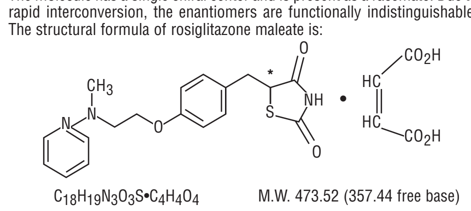
Limited data are available with regard to overdosage in humans. In clinical trials in volunteers, rosiglitazone maleate has been administered at single oral doses of up to 20 mg and was well-tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the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

11 DESCRIPTION

Rosiglitazone maleate is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. Rosiglitazone maleate improves glycemic control while reducing circulating insulin levels.

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

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



$C_{18}H_{19}N_3O_3S \bullet C_4H_4O_4$ M.W. 473.52 (357.44 free base)

Rosiglitazone maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pKa values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

Each round, standard-convex, coated tablet contains rosiglitazone maleate equivalent to rosiglitazone, 2 mg, 4 mg, or 8 mg, for oral administration. Inactive ingredients are: croscarmellose sodium, hypromellose (2910, 6cP), iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, titanium dioxide, and triacetin. In addition, the 2 mg tablet contains FD&C blue #2 (indigo carmine aluminum lake), the 4 mg tablet contains iron oxide black, and the 4 mg and 8 mg tablets contain iron oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

12.2 Pharmacodynamics

Patients with lipid abnormalities were not excluded from clinical trials of rosiglitazone maleate. In all 26 week controlled trials, across the recommended dose range, rosiglitazone maleate as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids. These changes were statistically significantly different from placebo or glyburide controls (**Table 9**).

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

The pattern of LDL and HDL changes following therapy with rosiglitazone maleate in combination with other hypoglycemic agents were generally similar to those seen with rosiglitazone maleate in monotherapy.

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

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

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

[a] Once daily and twice daily dosing groups were combined.

12.3 Pharmacokinetics

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

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

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

[a] CL/F = Oral clearance.

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

__Distribution:__ The mean (CV%) oral volume of distribution (Vss/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

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

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

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

__Population Pharmacokinetics in Patients With Type 2 Diabetes:__ Population pharmacokinetic analyses from 3 large clinical trials including 642 men and 405 women with type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume of distribution (Vss/F) were shown to increase with increases in body weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted CL/F and Vss/F values varied by < 1.7 fold and < 2.3 fold, respectively. Additionally, rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about 15%) in female patients.

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

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

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

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

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

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

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

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

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

12.4 Drug-Drug Interactions

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

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

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

__Glyburide:__ Rosiglitazone (2 mg twice daily) taken concomitantly with glyburide (3.75 to 10 mg/day) for 7 days did not alter the mean steady-state 24 hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy. Repeat doses of rosiglitazone (8 mg once daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and C_{max} of approximately 30%. In Japanese subjects, glyburide AUC and C_{max} slightly increased following coadministration of rosiglitazone maleate.

__Glimepiride:__ Single oral doses of glimepiride in 14 healthy adult subjects had no clinically significant effect on the steady-state pharmacokinetics of rosiglitazone maleate. No clinically significant reductions in glimepiride AUC and C_{max} were observed after repeat doses of rosiglitazone (8 mg once daily) for 8 days in healthy adult subjects.

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

__Acarbose:__ Coadministration of acarbose (100 mg three times daily) for 7 days in healthy volunteers had no clinically relevant effect on the pharmacokinetics of a single oral dose of rosiglitazone maleate.

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

__Warfarin:__ Repeat dosing with rosiglitazone maleate had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers.

__Ethanol:__ A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in type 2 diabetes mellitus patients treated with rosiglitazone maleate.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Monotherapy

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

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

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

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

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

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

[a] $P < 0.0001$ compared to placebo.

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

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

The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a statistically significant improvement in glycemic control from baseline (**Figure 3** and **Figure 4**). At the end of week 52, the reduction from baseline in FPG and HbA1c was -40.8 mg/dL and -0.53% with rosiglitazone 4 mg twice daily; -25.4 mg/dL and -0.27% with rosiglitazone 2 mg twice daily; and -30.0 mg/dL and -0.72% with glyburide. For HbA1c, the difference between rosiglitazone 4 mg twice daily and glyburide was not statistically significant at week 52. The initial fall in FPG with glyburide was greater than with rosiglitazone maleate; however, this effect was less durable over time. The improvement in glycemic control seen with rosiglitazone 4 mg twice daily at week 26 was maintained through week 52 of the trial.

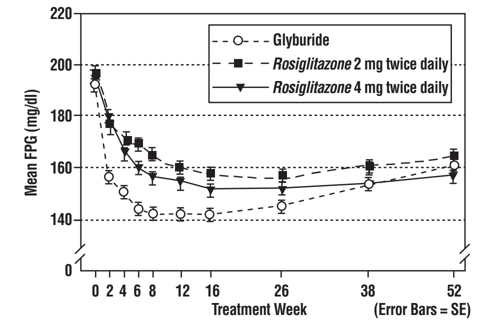


Figure 3. Mean FPG Over Time in a 52 Week Glyburide-Controlled Trial

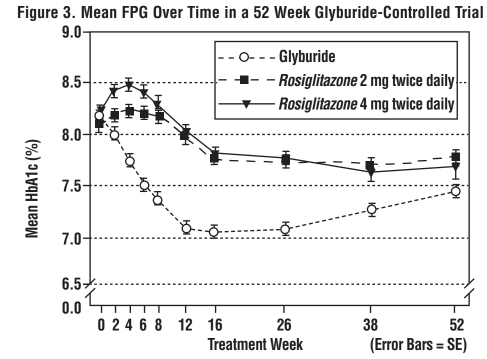


Figure 4. Mean HbA1c Over Time in a 52 Week Glyburide-Controlled Trial

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

A Diabetes Outcome Progression Trial (ADOPT) was a multicenter, double-blind, controlled trial (N = 4,351) conducted over 4 to 6 years to compare the safety and efficacy of rosiglitazone maleate, metformin, and glyburide monotherapy in patients recently diagnosed with type 2 diabetes mellitus (≤ 3 years) inadequately controlled with diet and exercise. The mean age of patients in this trial was 57 years and the majority of patients (83%) had no known history of cardiovascular disease. The mean baseline FPG and HbA1c were 152 mg/dL and 7.4%, respectively. Patients were randomized to receive either rosiglitazone 4 mg once daily, glyburide 2.5 mg once daily, or metformin 500 mg once daily, and doses were titrated to optimal glycemic control up to a maximum of 4 mg twice daily for rosiglitazone, 7.5 mg twice daily for glyburide, and 1,000 mg twice daily for metformin. The primary efficacy outcome was time to consecutive FPG > 180 mg/dL after at least 6 weeks of treatment at the maximum tolerated dose of study medication or time to inadequate glycemic control, as determined by an independent adjudication committee.

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

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

14.2 Combination With Metformin or Sulfonylurea

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

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

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

Table 12. Glycemic Parameters in a 26 Week Combination Trial of Rosiglitazone Maleate Plus Metformin

	Metformin	Rosiglitazone 4 mg once daily + metformin	Rosiglitazone 8 mg once daily + metformin
	N = 113	N = 116	N = 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 ≥ 0.7% decrease from baseline	11%	45%	52%

[a] $P < 0.0001$ compared to metformin.

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

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

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

In these trials, the combination of rosiglitazone 4 mg or 8 mg daily (administered as single or twice daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c compared to placebo plus sulfonylurea or further up-titration of the sulfonylurea. **Table 13** shows pooled data for 8 trials in which rosiglitazone maleate added to sulfonylurea was compared to placebo plus sulfonylurea.

Table 13. Glycemic Parameters in 24 to 26 Week Combination Trials of Rosiglitazone Maleate Plus Sulfonylurea

Twice Daily Divided Dosing (5 Studies)	Sulfonylurea	Rosiglitazone 2 mg twice daily + sulfonylurea	Sulfonylurea	Rosiglitazone 4 mg twice daily + sulfonylurea
	N = 397	N = 497	N = 248	N = 346
FPG (mg/dL)				
Baseline (mean)	204	198	188	187
Change from baseline (mean)	11	-29	8	-43
Difference from sulfonylurea alone (adjusted mean)	–	-42[a]	–	-53[a]
% of patients with ≥ 30 mg/dL decrease from baseline	17%	49%	15%	61%
HbA1c (%)				
Baseline (mean)	9.4	9.5	9.3	9.6
Change from baseline (mean)	0.2	-1.0	0.0	-1.6
Difference from sulfonylurea alone (adjusted mean)	–	-1.1[a]	–	-1.4[a]
% of patients with ≥ 0.7% decrease from baseline	21%	60%	23%	75%
Once Daily Dosing (3 Trials)	**Sulfonylurea**	**Rosiglitazone 4 mg once daily + sulfonylurea**	**Sulfonylurea**	**Rosiglitazone 8 mg once daily + sulfonylurea**
	N = 172	N = 172	N = 173	N = 176
FPG (mg/dL)				
Baseline (mean)	198	206	188	192
Change from baseline (mean)	17	-25	17	-43
Difference from sulfonylurea alone (adjusted mean)	–	-47[a]	–	-66[a]
% of patients with ≥ 30 mg/dL decrease from baseline	17%	48%	19%	55%
HbA1c (%)				
Baseline (mean)	8.6	8.8	8.9	8.9
Change from baseline (mean)	0.4	-0.5	0.1	-1.2
Difference from sulfonylurea alone (adjusted mean)	–	-0.9[a]	–	-1.4[a]
% of patients with ≥ 0.7% decrease from baseline	11%	36%	20%	68%

[a] $P < 0.0001$ compared to sulfonylurea alone.

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

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

14.3 Combination With Sulfonylurea Plus Metformin

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

Table 14. Glycemic Parameters in a 26 Week Combination Trial of Rosiglitazone Maleate Plus Sulfonylurea and Metformin

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

[a] $P < 0.0001$ compared to placebo.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

Each round, standard-convex, coated tablet contains rosiglitazone as the maleate as follows:

2 mg – pink tablets, debossed with the number "93" on one side and "7322" on the other. They are available in bottles of 60.

4 mg – orange tablets, debossed with the number "93" on one side and "7323" on the other. They are available in bottles of 30, 100, and 500.

8 mg – red-brown tablets, debossed with the number "93" on one side and "7324" on the other. They are available in bottles of 30, 100, and 500.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

17 PATIENT COUNSELING INFORMATION

See Medication Guide.

17.1 Patient Advice

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

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

Patients should be informed of the following:

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

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TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 8/2012

MEDICATION GUIDE

Rosiglitazone Maleate Tablets

Read this Medication Guide carefully before you start taking rosiglitazone maleate tablets and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about rosiglitazone maleate tablets, ask your doctor or pharmacist.

What is the most important information I should know about rosiglitazone maleate tablets?

Rosiglitazone maleate tablets is available only through the AVANDIA-Rosiglitazone Medicines Access Program. Both you and your doctor must be enrolled in the program so that you can get rosiglitazone maleate tablets. To enroll, you must:

- talk to your doctor,
- understand all the risks and benefits of rosiglitazone maleate tablets, and
- agree to enroll in the program.

Rosiglitazone maleate tablets may cause serious side effects, including:

New or worse heart failure

- Rosiglitazone maleate tablets can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Heart failure means your heart does not pump blood well enough.
- If you have severe heart failure, you cannot start rosiglitazone maleate tablets.
- If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, rosiglitazone maleate tablets may not be right for you.

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

- swelling or fluid retention, especially in the ankles or legs
- shortness of breath or trouble breathing, especially when you lie down
- an unusually fast increase in weight
- unusual tiredness

Myocardial Infarction ("Heart Attack")

Rosiglitazone maleate tablets may raise the risk of a heart attack. The risk of having a heart attack may be higher in people who take rosiglitazone maleate tablets with insulin. Most people who take insulin should not also take rosiglitazone maleate tablets.

Symptoms of a heart attack can include the following:

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

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

People with diabetes have a greater risk for heart problems. It is important to work with your doctor to manage other conditions, such as high blood pressure or high cholesterol.

Rosiglitazone maleate tablets can have other serious side effects. Be sure to read the section below "**What are possible side effects of rosiglitazone maleate tablets?**"

What are rosiglitazone maleate tablets?

Rosiglitazone maleate tablets are a prescription medicine used with diet and exercise to treat certain adults with type 2 (adult-onset or non-insulin dependent) diabetes mellitus (high blood sugar) who are:

- already taking rosiglitazone maleate tablets or
- unable to control their blood sugar on other diabetes medicines, and after talking with their doctor have decided not to take pioglitazone (ACTOS®)

Rosiglitazone maleate tablets help to control high blood sugar. Rosiglitazone maleate tablets may be used alone or with other diabetes medicines. Rosiglitazone maleate tablets can help your body respond better to insulin made in your body. Rosiglitazone maleate tablets do not cause your body to make more insulin.

Rosiglitazone maleate tablets are not for people with type 1 diabetes mellitus or to treat a condition called diabetic ketoacidosis.

It is not known if rosiglitazone maleate tablets are safe and effective in children under 18 years old.

Who should not take rosiglitazone maleate tablets?

Many people with heart failure should not start taking rosiglitazone maleate tablets. See "**What should I tell my doctor before taking rosiglitazone maleate tablets?**".

What should I tell my doctor before taking rosiglitazone maleate tablets?

Before starting rosiglitazone maleate tablets, ask your doctor about what the choices are for diabetes medicines, and what the expected benefits and possible risks are for you in particular.

Before taking rosiglitazone maleate tablets, tell your doctor about all your medical conditions, including if you:

- **have heart problems or heart failure.**
- **have type 1 ("juvenile") diabetes or had diabetic ketoacidosis.** These conditions should be treated with insulin.
- **have a type of diabetic eye disease called macular edema** (swelling of the back of the eye).
- **have liver problems.** Your doctor should do blood tests to check your liver before you start taking rosiglitazone maleate tablets and during treatment as needed.
- **had liver problems while taking REZULIN® (troglitazone), another medicine for diabetes.**
- **are pregnant or plan to become pregnant.** Rosiglitazone maleate tablets should not be used during pregnancy. It is not known if rosiglitazone maleate tablets can harm your unborn baby. You and your doctor should talk about the best way to control your diabetes during pregnancy. If you are a premenopausal woman (before the "change of life") who does not have regular monthly periods, rosiglitazone maleate tablets may increase your chances of becoming pregnant. Talk to your doctor about birth control choices while taking rosiglitazone maleate tablets. Tell your doctor right away if you become pregnant while taking rosiglitazone maleate tablets.
- **are breast-feeding or planning to breast-feed.** It is not known if rosiglitazone maleate passes into breast milk. You should not use rosiglitazone maleate tablets while breast-feeding.

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

- **insulin.**
- **any medicines for high blood pressure, high cholesterol or heart failure, or for prevention of heart disease or stroke.**

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

How should I take rosiglitazone maleate tablets?

- Take rosiglitazone maleate tablets exactly as prescribed. Your doctor will tell you how many tablets to take and how often. The usual daily starting dose is 4 mg a day taken one time each day or 2 mg taken two times each day. Your doctor may need to adjust your dose until your blood sugar is better controlled.

- Rosiglitazone maleate tablets may be prescribed alone or with other diabetes medicines. This will depend on how well your blood sugar is controlled.
- Take rosiglitazone maleate tablets with or without food.
- It can take 2 weeks for rosiglitazone maleate tablets to start lowering blood sugar. It may take 2 to 3 months to see the full effect on your blood sugar level.
- If you miss a dose of rosiglitazone maleate tablets, take it as soon as you remember, unless it is time to take your next dose. Take your next dose at the usual time. Do not take double doses to make up for a missed dose.
- If you take too many rosiglitazone maleate tablets, call your doctor or poison control center right away.
- Test your blood sugar regularly as your doctor tells you.
- Diet and exercise can help your body use its blood sugar better. It is important to stay on your recommended diet, lose extra weight, and get regular exercise while taking rosiglitazone maleate tablets.
- Your doctor should do blood tests to check your liver before you start rosiglitazone maleate tablets and during treatment as needed. Your doctor should also do regular blood sugar tests (for example, "A1C") to monitor your response to rosiglitazone maleate tablets.

What are possible side effects of rosiglitazone maleate tablets?

Rosiglitazone maleate tablets may cause serious side effects including:

- **New or worse heart failure.** See **"What is the most important information I should know about rosiglitazone maleate tablets?".**
- **Heart attack.** See **"What is the most important information I should know about rosiglitazone maleate tablets?".**
- **Swelling (edema).** Rosiglitazone maleate tablets can cause swelling due to fluid retention. See "**What is the most important information I should know about rosiglitazone maleate tablets?**".
- **Weight gain.** Rosiglitazone maleate tablets can cause weight gain that may be due to fluid retention or extra body fat. Weight gain can be a serious problem for people with certain conditions including heart problems. See "**What is the most important information I should know about rosiglitazone maleate tablets?**".
- **Liver problems.** It is important for your liver to be working normally when you take rosiglitazone maleate tablets. Your doctor should do blood tests to check your liver before you start taking rosiglitazone maleate tablets and during treatment as needed. Call your doctor right away if you have unexplained symptoms such as:
  - nausea or vomiting
  - stomach pain
  - unusual or unexplained tiredness
  - loss of appetite
  - dark urine
  - yellowing of your skin or the whites of your eyes.
- **Macular edema** (a diabetic eye disease with swelling in the back of the eye). Tell your doctor right away if you have any changes in your vision. Your doctor should check your eyes regularly. Very rarely, some people have had vision changes due to swelling in the back of the eye while taking rosiglitazone maleate tablets.
- **Fractures (broken bones),** usually in the hand, upper arm or foot. Talk to your doctor for advice on how to keep your bones healthy.
- **Low red blood cell count (anemia).**
- **Low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness or hunger may mean that your blood sugar is too low. This can happen if you skip meals, if you use another medicine that lowers blood sugar, or if you have certain medical problems. Call your doctor if low blood sugar levels are a problem for you.
- **Ovulation** (release of egg from an ovary in a woman) leading to pregnancy. Ovulation may happen in premenopausal women who do not have regular monthly periods. This can increase the chance of pregnancy. See "**What should I tell my doctor before taking rosiglitazone maleate tablets?**".

The most common side effects of rosiglitazone maleate tablets reported in clinical trials included cold-like symptoms and headache.

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

How should I store rosiglitazone maleate tablets?

- Store rosiglitazone maleate tablets at room temperature, 20° to 25°C (68° to 77°F). Keep rosiglitazone maleate tablets in the container they come in.
- Safely, throw away rosiglitazone maleate tablets that are out of date or no longer needed.
- Keep rosiglitazone maleate tablets and all medicines out of the reach of children.

General information about rosiglitazone maleate tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use rosiglitazone maleate tablets for a condition for which they were not prescribed. Do not give rosiglitazone maleate tablets to other people, even if they have the same symptoms you have. They may harm them.

This Medication Guide summarizes important information about rosiglitazone maleate tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about rosiglitazone maleate tablets that is written for healthcare professionals. You can also find out more about rosiglitazone maleate tablets by calling Teva Pharmaceuticals at 1-888-838-2872, MEDICAL AFFAIRS.

What are the ingredients in rosiglitazone maleate tablets?

Active Ingredient: rosiglitazone maleate.

Inactive Ingredients: croscarmellose sodium, hypromellose (2910, 6cP), iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, titanium dioxide, and triacetin. In addition, the 2 mg tablet contains FD&C blue #2 (indigo carmine aluminum lake), the 4 mg tablet contains iron oxide black, and the 4 mg and 8 mg tablets contain iron oxide yellow.

Always check to make sure that the medicine you are taking is the correct one. Rosiglitazone maleate tablets are round and standard-convex and look like this:

2 mg – pink with "93" on one side and "7322" on the other.

4 mg – orange with "93" on one side and "7323" on the other.

8 mg – red-brown with "93" on one side and "7324" on the other.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Iss. 11/2011

MEDICATION GUIDE

Rosiglitazone Maleate Tablets

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- talk to your doctor,
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Rosiglitazone maleate tablets may cause serious side effects, including:

New or worse heart failure

- Rosiglitazone maleate tablets can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Heart failure means your heart does not pump blood well enough.
- If you have severe heart failure, you cannot start rosiglitazone maleate tablets.
- If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, rosiglitazone maleate tablets may not be right for you.

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

- swelling or fluid retention, especially in the ankles or legs
- shortness of breath or trouble breathing, especially when you lie down
- an unusually fast increase in weight
- unusual tiredness

Myocardial Infarction ("Heart Attack")

Rosiglitazone maleate tablets may raise the risk of a heart attack. The risk of having a heart attack may be higher in people who take rosiglitazone maleate tablets with insulin. Most people who take insulin should not also take rosiglitazone maleate tablets.

Symptoms of a heart attack can include the following:

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

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

People with diabetes have a greater risk for heart problems. It is important to work with your doctor to manage other conditions, such as high blood pressure or high cholesterol.

Rosiglitazone maleate tablets can have other serious side effects. Be sure to read the section below "**What are possible side effects of rosiglitazone maleate tablets?**"

What are rosiglitazone maleate tablets?

Rosiglitazone maleate tablets are a prescription medicine used with diet and exercise to treat certain adults with type 2 (adult-onset or non-insulin dependent) diabetes mellitus (high blood sugar) who are:

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- unable to control their blood sugar on other diabetes medicines, and after talking with their doctor have decided not to take pioglitazone (ACTOS®)

Rosiglitazone maleate tablets help to control high blood sugar. Rosiglitazone maleate tablets may be used alone or with other diabetes medicines. Rosiglitazone maleate tablets can help your body respond better to insulin made in your body. Rosiglitazone maleate tablets do not cause your body to make more insulin.

Rosiglitazone maleate tablets are not for people with type 1 diabetes mellitus or to treat a condition called diabetic ketoacidosis.

It is not known if rosiglitazone maleate tablets are safe and effective in children under 18 years old.

Who should not take rosiglitazone maleate tablets?

Many people with heart failure should not start taking rosiglitazone maleate tablets. See "**What should I tell my doctor before taking rosiglitazone maleate tablets?**".

What should I tell my doctor before taking rosiglitazone maleate tablets?

Before starting rosiglitazone maleate tablets, ask your doctor about what the choices are for diabetes medicines, and what the expected benefits and possible risks are for you in particular.

Before taking rosiglitazone maleate tablets, tell your doctor about all your medical conditions, including if you:

- **have heart problems or heart failure.**
- **have type 1 ("juvenile") diabetes or had diabetic ketoacidosis.** These conditions should be treated with insulin.
- **have a type of diabetic eye disease called macular edema** (swelling of the back of the eye).
- **have liver problems.** Your doctor should do blood tests to check your liver before you start taking rosiglitazone maleate tablets and during treatment as needed.
- **had liver problems while taking REZULIN® (troglitazone), another medicine for diabetes.**
- **are pregnant or plan to become pregnant.** Rosiglitazone maleate tablets should not be used during pregnancy. It is not known if rosiglitazone maleate tablets can harm your unborn baby. You and your doctor should talk about the best way to control your diabetes during pregnancy. If you are a premenopausal woman (before the "change of life") who does not have regular monthly periods, rosiglitazone maleate tablets may increase your chances of becoming pregnant. Talk to your doctor about birth control choices while taking rosiglitazone maleate tablets. Tell your doctor right away if you become pregnant while taking rosiglitazone maleate tablets.
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Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins or herbal supplements. Rosiglitazone maleate tablets and certain other medicines can affect each other and may lead to serious side effects including high or low blood sugar, or heart problems. Especially tell your doctor if you take:

- **insulin.**
- **any medicines for high blood pressure, high cholesterol or heart failure, or for prevention of heart disease or stroke.**

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

How should I take rosiglitazone maleate tablets?

- Take rosiglitazone maleate tablets exactly as prescribed. Your doctor will tell you how many tablets to take and how often. The usual daily starting dose is 4 mg a day taken one time each day or 2 mg taken two times each day. Your doctor may need to adjust your dose until your blood sugar is better controlled.

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- Take rosiglitazone maleate tablets with or without food.
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Rosiglitazone maleate tablets may cause serious side effects including:

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- **Macular edema** (a diabetic eye disease with swelling in the back of the eye). Tell your doctor right away if you have any changes in your vision. Your doctor should check your eyes regularly. Very rarely, some people have had vision changes due to swelling in the back of the eye while taking rosiglitazone maleate tablets.
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Inactive Ingredients: croscarmellose sodium, hypromellose (2910, 6cP), iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, titanium dioxide, and triacetin. In addition, the 2 mg tablet contains FD&C blue #2 (indigo carmine aluminum lake), the 4 mg tablet contains iron oxide black, and the 4 mg and 8 mg tablets contain iron oxide yellow.

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8 mg – red-brown with "93" on one side and "7324" on the other.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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