NDC 0093-7643-56

once daily

Rosiglitazone Maleate and Glimepiride Tablets

4 mg*/1 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 and contains 1 mg glimepiride, USP.

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, 9777402, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA, INC.
North Wales, PA 19454

Iss. 9/2015

N 3 0093-7643-56 2

NDC 0093-7643-05

once daily

Rosiglitazone Maleate and Glimepiride Tablets

4 mg*/1 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 and contains 1 mg glimepiride, USP.

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).

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Iss. 9/2015

N 3 0093-7643-05 0

NDC 0093-7644-56

once daily

Rosiglitazone Maleate and Glimepiride Tablets

4 mg*/2 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 and contains 2 mg glimepiride, USP.

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).

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NDC 0093-7644-05

once daily

Rosiglitazone Maleate and Glimepiride Tablets

4 mg*/2 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 and contains 2 mg glimepiride, USP.

Usual Dosage: See package insert for full prescribing information.

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Iss. 9/2015

N 3 0093-7644-05 7

NDC 0093-7642-56

once daily

Rosiglitazone Maleate and Glimepiride Tablets

4 mg*/4 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. 9/2015

N 3 0093-7642-56 5

NDC 0093-7642-05

once daily

Rosiglitazone Maleate and Glimepiride Tablets

4 mg*/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 and contains 4 mg glimepiride, USP.

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).

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Iss. 9/2015

N 3 0093-7642-05 3

NDC 0093-7700-56

once daily

Rosiglitazone Maleate and Glimepiride Tablets

8 mg*/2 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

30 TABLETS

TEVA

* Each film-coated tablet contains rosiglitazone maleate equivalent to 8 mg rosiglitazone and contains 2 mg glimepiride, USP.

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).

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North Wales, PA 19454

Iss. 9/2015

N 3 0093-7700-56 2

NDC 0093-**7700**-05

once daily

Rosiglitazone Maleate and Glimepiride Tablets

8 mg*/2 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

500 TABLETS

TEVA

* Each film-coated tablet contains rosiglitazone maleate equivalent to 8 mg rosiglitazone and contains 2 mg glimepiride, USP.

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).

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Iss. 9/2015

N 3 0093-7700-05 0

NDC 0093-7702-56

once daily

Rosiglitazone Maleate and Glimepiride Tablets

8 mg*/4 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

30 TABLETS

TEVA

* Each film-coated tablet contains rosiglitazone maleate equivalent to 8 mg rosiglitazone and contains 4 mg glimepiride, USP.

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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North Wales, PA 19454

Iss. 9/2015

N 3 0093-7702-56 6

NDC 0093-**7702**-05

once daily

Rosiglitazone Maleate and Glimepiride Tablets

8 mg*/4 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

500 TABLETS

TEVA

*Each film-coated tablet contains rosiglitazone maleate equivalent to 8 mg rosiglitazone and contains 4 mg glimepiride, USP.

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).

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Iss. 9/2015

N 3 0093-7702-05 4

ROSIGLITAZONE MALEATE AND GLIMEPIRIDE TABLETS

7643
7644
7642
7700
7702

℞ only

Iss. 9/2015

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ROSIGLITAZONE MALEATE AND GLIMEPIRIDE TABLETS safely and effectively. See full prescribing information for ROSIGLITAZONE MALEATE AND GLIMEPIRIDE TABLETS.

ROSIGLITAZONE MALEATE and GLIMEPIRIDE tablets, for oral use

Initial U.S. Approval: 2005

WARNING: CONGESTIVE HEART FAILURE
See full prescribing information for complete boxed warning.

- **Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (5.1). After initiation of rosiglitazone maleate and glimepiride 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 and glimepiride tablets must be considered.**
- **Rosiglitazone maleate and glimepiride tablets are not recommended in patients with symptomatic heart failure. Initiation of rosiglitazone maleate and glimepiride tablets in patients with established NYHA Class III or IV heart failure is contraindicated (4, 5.1).**

---------- RECENT MAJOR CHANGES ----------

Boxed Warning, Rosiglitazone Maleate and Glimepiride Tablets -Rosiglitazone Medicines Access Program removal	05/2014
Indications and Usage, patient population restrictions removal (1)	05/2014
Dosage and Administration (2)	05/2014
Contraindications (4)	05/2014
Warnings and Precautions, Cardiac Failure (5.1)	05/2014
Warnings and Precautions, Major Adverse Cardiovascular Events (5.2)	05/2014
Warnings and Precautions, Rosiglitazone REMS (Risk Evaluation and Mitigation Strategy) Program removal (formerly 5.4)	05/2014
Warnings and Precautions, Weight Gain (5.5)	05/2014
Warnings and Precautions, Hypersensitivity Reactions (5.9)	03/2015

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

Rosiglitazone maleate and glimepiride tablets are a combination antidiabetic product containing a thiazolidinedione and a sulfonylurea indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. (1)

Important Limitations of Use:

- Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. (1, 4)
- Coadministration with insulin is not recommended. (1, 5.1, 5.2)

--------- DOSAGE AND ADMINISTRATION ---------

- Individualize the starting dose based on the patient's current regimen. (2.1)
- Administer rosiglitazone maleate and glimepiride tablets at least 4 hours prior to colesevelam. (2.1)
- Dose increases should be accompanied by careful monitoring for adverse events related to fluid retention. (2.2)
- Do not exceed the maximum recommended daily dose of 8 mg rosiglitazone and 4 mg glimepiride. (2.3)
- Do not initiate if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels. (2.4)

-------- DOSAGE FORMS AND STRENGTHS --------

Standard convex tablets containing rosiglitazone/glimepiride: 4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg, 8 mg/2 mg, and 8 mg/4 mg (3)

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

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

--------- WARNINGS AND PRECAUTIONS ---------

- Fluid retention, which may exacerbate or lead to heart failure, may occur. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk of other cardiovascular effects. (5.1)
- Meta-analysis of 52 mostly short-term trials suggested a potential risk of ischemic cardiovascular (CV) events relative to placebo, not confirmed in a long-term CV outcome trial versus metformin or sulfonylurea. (5.2)
- Severe hypoglycemia may occur. Use particular care in elderly or debilitated patients and those with adrenal, pituitary, renal, or hepatic insufficiency. (5.3)
- Dose-related edema (5.4), weight gain (5.5), and anemia (5.10) may occur.
- Macular edema has been reported. (5.7)
- Increased incidence of bone fracture. (5.8)
- Postmarketing reports for glimepiride include anaphylaxis, angioedema, and Stevens-Johnson syndrome. Promptly discontinue rosiglitazone maleate and glimepiride tablets, assess for other causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.9)
- Hemolytic anemia can occur if glucose 6-phosphate dehydrogenase (G6PD) deficient. Consider a non-sulfonylurea alternative. (5.11)
- Potential increased risk of cardiovascular mortality with sulfonylureas: Inform patients of risks, benefits and treatment alternatives. (5.12)

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

Common adverse reactions (≥ 5%) reported in clinical trials for rosiglitazone maleate and glimepiride tablets without regard to causality were headache, hypoglycemia, and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TEVA USA, PHARMACOVIGILANCE at 1-866-832-8537 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. (7.1)
- Inducers of CYP2C8 (e.g., rifampin) may decrease rosiglitazone levels. (7.1)
- Inhibitors and inducers of CYP2C9 may affect glycemic control by altering glimepiride plasma concentrations. (7.1)
- Certain medications may affect glucose metabolism, requiring glimepiride dose adjustment and close monitoring of blood glucose. (7.2)
- Miconazole: Severe hypoglycemia can occur when glimepiride and oral miconazole are used concomitantly. (7.3)
- Colesevelam: Coadministration may reduce glimepiride absorption. Rosiglitazone maleate and glimepiride tablets should be administered at least 4 hours prior to colesevelam. (2.1, 7.4)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: No adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- Nursing Mothers: Discontinue drug or nursing (8.3)
- Safety and effectiveness in children younger than 18 years have not been established. (8.4)
- Elderly patients may be particularly susceptible to hypoglycemic effects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: CONGESTIVE HEART FAILURE

- **Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients *[see Warnings and Precautions (5.1)]*. After initiation of rosiglitazone maleate and glimepiride 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 and glimepiride tablets must be considered.**
- **Rosiglitazone maleate and glimepiride tablets are not recommended in patients with symptomatic heart failure. Initiation of rosiglitazone maleate and glimepiride tablets in patients with established NYHA Class III or IV heart failure is contraindicated *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

Rosiglitazone maleate and glimepiride tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Important Limitations of Use:

- Due to its mechanism of action, rosiglitazone is active only in the presence of endogenous insulin. Therefore, rosiglitazone maleate and glimepiride tablets should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
- Coadministration of rosiglitazone maleate and glimepiride tablets with insulin is not recommended *[see Warnings and Precautions (5.1, 5.2)]*.

2 DOSAGE AND ADMINISTRATION

Therapy with rosiglitazone maleate and glimepiride tablets should be individualized for each patient. The risk-benefit of initiating monotherapy versus dual therapy with rosiglitazone maleate and glimepiride tablets should be considered.

No studies have been performed specifically examining the safety and efficacy of rosiglitazone maleate and glimepiride tablets in patients previously treated with other oral hypoglycemic agents and switched to rosiglitazone maleate and glimepiride tablets. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur *[see Indications and Usage (1)]*.

2.1 Starting Dose

The recommended starting dose is 4 mg/1 mg administered once daily with the first meal of the day. For adults already treated with a sulfonylurea or rosiglitazone, a starting dose of 4 mg/2 mg may be considered.

All patients should start the rosiglitazone component of rosiglitazone maleate and glimepiride tablets at the lowest recommended dose. Further increases in the dose of rosiglitazone should be accompanied by careful monitoring for adverse events related to fluid retention *[see Boxed Warning, Warnings and Precautions (5.1)]*.

When switching from combination therapy of rosiglitazone plus glimepiride as separate tablets, the usual starting dose of rosiglitazone maleate and glimepiride tablets is the dose of rosiglitazone and glimepiride already being taken.

When colesevelam is coadministered with glimepiride, maximum plasma concentration and total exposure to glimepiride is reduced. Therefore, rosiglitazone maleate and glimepiride tablets should be administered at least 4 hours prior to colesevelam.

2.2 Dose Titration

Dose increases should be individualized according to the glycemic response of the patient. Patients who may be more sensitive to glimepiride *[see Warnings and Precautions (5.3)]*, including the elderly, debilitated, or malnourished, and those with renal, hepatic, or adrenal insufficiency, should be carefully titrated to avoid hypoglycemia. If hypoglycemia occurs during up-titration of the dose or while maintained on therapy, a dosage reduction of the glimepiride component of rosiglitazone maleate and glimepiride tablets may be considered. Increases in the dose of rosiglitazone should be accompanied by careful monitoring for adverse events related to fluid retention *[see Boxed Warning, Warnings and Precautions (5.1)]*.

To switch to rosiglitazone maleate and glimepiride tablets for adults currently treated with rosiglitazone, dose titration of the glimepiride component of rosiglitazone maleate and glimepiride tablets is recommended if patients are not adequately controlled after 1 to 2 weeks. The glimepiride component may be increased in no more than 2 mg increments. After an increase in the dosage of the glimepiride component, dose titration of rosiglitazone maleate and glimepiride tablets is recommended if patients are not adequately controlled after 1 to 2 weeks.

To switch to rosiglitazone maleate and glimepiride tablets for adults currently treated with sulfonylurea, it may take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of the rosiglitazone component. Therefore, dose titration of the rosiglitazone component of rosiglitazone maleate and glimepiride tablets is recommended if patients are not adequately controlled after 8 to 12 weeks. Patients should be observed carefully (1 to 2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to rosiglitazone maleate and glimepiride tablets due to potential overlapping of drug effect. After an increase in the dosage of the rosiglitazone component, dose titration of rosiglitazone maleate and glimepiride tablets is recommended if patients are not adequately controlled after 2 to 3 months.

2.3 Maximum Dose

The maximum recommended daily dose is 8 mg rosiglitazone and 4 mg glimepiride.

2.4 Specific Patient Populations

Elderly and Malnourished Patients and Those With Renal, Hepatic, or Adrenal Insufficiency: In elderly, debilitated, or malnourished patients, or in patients with renal, hepatic, or adrenal insufficiency, the starting dose, dose increments, and maintenance dosage of rosiglitazone maleate and glimepiride tablets should be conservative to avoid hypoglycemic reactions *[see Warnings and Precautions (5.3), Clinical Pharmacology (12.3)]*.

Hepatic Impairment: Liver enzymes should be measured prior to initiating treatment with rosiglitazone maleate and glimepiride tablets. Therapy with rosiglitazone maleate and glimepiride 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 and glimepiride tablets, liver enzymes should be monitored periodically per the clinical judgment of the healthcare professional *[see Warnings and Precautions (5.6), Clinical Pharmacology (12.3)]*.

Pregnancy and Lactation: Rosiglitazone maleate and glimepiride tablets should not be used during pregnancy or in nursing mothers.

Pediatric Use: Safety and effectiveness of rosiglitazone maleate and glimepiride tablets in pediatric patients have not been established. Rosiglitazone maleate and glimepiride tablets and their components, rosiglitazone and glimepiride, are not recommended for use in pediatric patients.

3 DOSAGE FORMS AND STRENGTHS

Rosiglitazone maleate and glimepiride tablets are available as follows:

- 4 mg/1 mg - yellow, film-coated, standard convex tablet, debossed with "93" on one side of the tablet and with "7643" on the other side.
- 4 mg/2 mg - orange, film-coated, standard convex tablet, debossed with "93" on one side of the tablet and with "7644" on the other side.
- 4 mg/4 mg - pink, film-coated, standard convex tablet, debossed with "93" on one side of the tablet and with "7642" on the other side.
- 8 mg/2 mg - pink, film-coated, standard convex tablet, debossed with "93" on one side of the tablet and with "7700" on the other side.
- 8 mg/4 mg - red, film-coated, standard convex tablet, debossed with "93" on one side of the tablet and with "7702" on the other side.

4 CONTRAINDICATIONS

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

Rosiglitazone maleate and glimepiride tablets are contraindicated in patients with a history of a hypersensitivity reaction to rosiglitazone or glimepiride or any of the product's ingredients.

Patients who have developed an allergic reaction to sulfonamide derivatives may develop an allergic reaction to rosiglitazone maleate and glimepiride tablets. Do not use rosiglitazone maleate and glimepiride tablets in patients who have a history of an allergic reaction to sulfonamide derivatives. Reported hypersensitivity reactions include cutaneous eruptions with or without pruritis as well as more serious reactions (e.g., anaphylaxis, angioedema, Stevens-Johnson syndrome, dyspnea) *[see Warnings and Precautions (5.9) and Adverse Reactions (6.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Failure With Rosiglitazone

Rosiglitazone, 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 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 with rosiglitazone treatment compared with 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 or Placebo (in Addition to Background Antidiabetic and CHF Therapy)

Events	Rosiglitazone N = 110 n (%)	Placebo 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[1]	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%)

1. Includes hospitalization for any cardiovascular reason.

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

Initiation of rosiglitazone maleate and glimepiride tablets in patients with established NYHA Class III or IV heart failure is contraindicated. Rosiglitazone maleate and glimepiride 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 and glimepiride tablets are not recommended for patients experiencing an acute coronary event, and discontinuation of rosiglitazone maleate and glimepiride tablets 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 and glimepiride tablets are not recommended in patients with NYHA Class III and IV cardiac status.

Congestive Heart Failure During Coadministration of Rosiglitazone With Insulin: In trials in which rosiglitazone was added to insulin, rosiglitazone increased the risk of congestive heart failure. Coadministration of rosiglitazone and insulin is not recommended *[see Indications and Usage (1), 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 *[see Warnings and Precautions (5.2)]*, patients with type 2 diabetes mellitus were randomized to coadministration of rosiglitazone and insulin (N = 1,018) or insulin (N = 815). In these 7 trials, rosiglitazone 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 plus insulin and insulin groups, respectively.

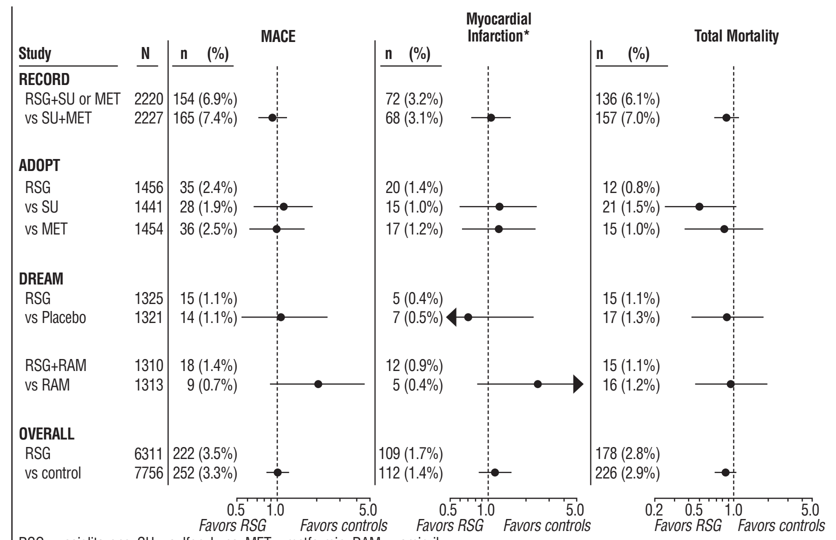
Heart Failure in Observational Studies of Elderly Diabetic Patients Comparing Rosiglitazone to Pioglitazone: Three observational studies in elderly diabetic patients (age 65 years and older) found that rosiglitazone statistically significantly increased the risk of hospitalized heart failure compared to use of pioglitazone. One other observational study 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 compared to pioglitazone in the older subgroup.

5.2 Major Adverse Cardiovascular Events

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

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

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



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

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

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

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

5.3 Hypoglycemia

Rosiglitazone maleate and glimepiride tablets are a combination tablet containing rosiglitazone and glimepiride, a sulfonylurea. All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs. Debilitated or malnourished patients, and those with adrenal, pituitary, renal, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. A starting dose of 1 mg glimepiride, as contained in rosiglitazone maleate and glimepiride tablets 4 mg/1 mg, followed by appropriate dose titration is recommended in these patients *[see Clinical Pharmacology (12.3)]*. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Patients receiving rosiglitazone in combination with a sulfonylurea may be at risk for hypoglycemia, and a reduction in the dose of the sulfonylurea may be necessary *[see Dosage and Administration (2.2)]*.

5.4 Edema

Rosiglitazone maleate and glimepiride tablets 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 with placebo.

Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, rosiglitazone maleate and glimepiride tablets 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), 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, and may be dose-related. Patients with ongoing edema were more likely to have adverse events associated with edema if started on combination therapy with insulin and rosiglitazone *[see Adverse Reactions (6.1)]*. The use of rosiglitazone maleate and glimepiride tablets in combination with insulin is not recommended *[see Warnings and Precautions (5.1, 5.2)]*.

5.5 Weight Gain

Dose-related weight gain was seen with rosiglitazone maleate and glimepiride tablets, rosiglitazone alone, and rosiglitazone together with other hypoglycemic agents (see Table 2). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 2. Weight Changes (kg) From Baseline at Endpoint During Clinical Trials [Median (25^{th}, 75^{th} Percentiles]

Duration	Control Group		Rosiglitazone 4 mg	Rosiglitazone 8 mg
Monotherapy				
26 weeks	Placebo	-0.9 (-2.8, 0.9) N = 210	1.0 (-0.9, 3.6) N = 436	3.1 (1.1, 5.8) N = 439
52 weeks	Sulfonylurea	2.0 (0, 4.0) N = 173	2.0 (-0.6, 4.0) N = 150	2.6 (0, 5.3) N = 157
Combination Therapy			**Rosiglitazone + Control Therapy**	
Duration	**Control Group**		**Rosiglitazone 4 mg**	**Rosiglitazone 8 mg**
24 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
26 weeks	Metformin	-1.4 (-3.2, 0.2) N = 175	0.8 (-1.0, 2.6) N = 100	2.1 (0, 4.3) N = 184
26 weeks	Insulin	0.9 (-0.5, 2.7) N = 162	4.1 (1.4, 6.3) N = 164	5.4 (3.4, 7.3) N = 150
Rosiglitazone Maleate and Glimepiride Tablets in Patients With Inadequate Control on Diet and Exercise				
Duration	**Control Group**		**Rosiglitazone Maleate and Glimepiride Tablets 4 mg/4 mg**	**Rosiglitazone Maleate and Glimepiride Tablets 8 mg/4 mg**
28 weeks	Glimepiride	1.1 (-1.1, 3.2) N = 222	2.2 (0, 4.5) N = 221	2.9 (0, 5.8) N = 217
	Rosiglitazone	0.9 (-1.4, 3.2) N = 228		

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

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

5.6 Hepatic Effects

With sulfonylureas, including glimepiride, there may be an elevation of liver enzyme levels in rare cases. In isolated instances, impairment of liver function (e.g., with cholestasis and jaundice), as well as hepatitis (which may also lead to liver failure) have been reported.

Liver enzymes should be measured prior to the initiation of therapy with rosiglitazone maleate and glimepiride tablets in all patients and periodically thereafter per the clinical judgment of the healthcare professional. Therapy with rosiglitazone maleate and glimepiride tablets 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 and glimepiride tablets should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with rosiglitazone maleate and glimepiride tablets in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent 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 and glimepiride tablets, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain > 3X the upper limit of normal, therapy with rosiglitazone maleate and glimepiride tablets 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 and glimepiride tablets should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

5.7 Macular Edema

Macular edema has been reported in postmarketing experience in some diabetic patients who were taking rosiglitazone 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 (6.3)]*.

5.8 Fractures

Long-term trials (ADOPT and RECORD) show an increased incidence of bone fracture in patients, particularly female patients, taking rosiglitazone *[see Adverse Reactions (6.1)]*. 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 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, and attention given to assessing and maintaining bone health according to current standards of care.

5.9 Hypersensitivity Reactions

There have been postmarketing reports of hypersensitivity reactions in patients treated with glimepiride, including serious reactions such as anaphylaxis, angioedema, and Stevens-Johnson syndrome. If a hypersensitivity reaction is suspected, promptly discontinue rosiglitazone maleate and glimepiride tablets, assess for other potential causes for the reaction, and institute alternative treatment for diabetes.

5.10 Hematologic Effects

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

5.11 Hemolytic Anemia

Sulfonylureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because glimepiride, a component of rosiglitazone maleate and glimepiride tablets, is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a nonsulfonylurea alternative. There are also postmarketing reports of hemolytic anemia in patients receiving glimepiride who did not have known G6PD deficiency *[see Adverse Reactions (6.3)]*.

5.12 Increased Risk of Cardiovascular Mortality With Sulfonylureas

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups.

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glimepiride and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

5.13 Diabetes and Blood Glucose Control

When a patient stabilized on any antidiabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold rosiglitazone maleate and glimepiride tablets and temporarily administer insulin. Rosiglitazone maleate and glimepiride tablets may be reinstituted after the acute episode is resolved.

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

5.14 Ovulation

Therapy with rosiglitazone, 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 *[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 and glimepiride tablets should be reviewed.

6 ADVERSE REACTIONS

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

- Cardiac Failure With Rosiglitazone *[see Warnings and Precautions (5.1)]*
- Major Adverse Cardiovascular Events *[see Warnings and Precautions (5.2)]*
- Hypoglycemia *[see Warnings and Precautions (5.3)]*
- Edema *[see Warnings and Precautions (5.4)]*
- Weight Gain *[see Warnings and Precautions (5.5)]*
- Hepatic Effects *[see Warnings and Precautions (5.6)]*
- Macular Edema *[see Warnings and Precautions (5.7)]*
- Fractures *[see Warnings and Precautions (5.8)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.9)]*
- Hematologic Effects *[see Warnings and Precautions (5.10)]*
- Hemolytic Anemia *[see Warnings and Precautions (5.11)]*
- Increased Risk of Cardiovascular Mortality for Sulfonylurea Drugs *[see Warnings and Precautions (5.12)]*
- Ovulation *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trial Experience

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

Patients With Inadequate Glycemic Control on Diet and Exercise: **Table 3** summarizes adverse events occurring at a frequency of ≥ 5% in any treatment group in the 28-week, double-blind trial of rosiglitazone maleate and glimepiride tablets in patients with type 2 diabetes mellitus inadequately controlled on diet and exercise. Patients in this trial were started on rosiglitazone maleate and glimepiride tablets 4 mg/1 mg, rosiglitazone 4 mg, or glimepiride 1 mg. Doses could be increased at 4-week intervals to reach a maximum total daily dose of either 4 mg/4 mg or 8 mg/4 mg for rosiglitazone maleate and glimepiride tablets, 8 mg for rosiglitazone monotherapy, or 4 mg for glimepiride monotherapy.

Table 3. Adverse Events (≥ 5% in any Treatment Group) Reported by Patients With Inadequate Glycemic Control on Diet and Exercise in a 28-Week, Double-blind Clinical Trial of Rosiglitazone Maleate and Glimepiride Tablets

Preferred Term	Glimepiride Monotherapy N = 222 %	Rosiglitazone Monotherapy N = 230 %	Rosiglitazone Maleate and Glimepiride Tablets 4 mg/4 mg N = 224 %	Rosiglitazone Maleate and Glimepiride Tablets 8 mg/4 mg N = 218 %
Headache	2.3	6.1	3.1	6.0
Nasopharyngitis	3.6	5.2	4.0	4.6
Hypertension	3.6	5.2	3.1	2.3
Hypoglycemia[1]	4.1	0.4	3.6	5.5

1. As documented by symptoms and a fingerstick blood glucose measurement of < 50 mg/dL.

Hypoglycemia was reported to be generally mild to moderate in intensity and none of the reported events of hypoglycemia resulted in withdrawal from the trial. Hypoglycemia requiring parenteral treatment (i.e., intravenous glucose or glucagon injection) was observed in 3 (0.7%) patients treated with rosiglitazone maleate and glimepiride tablets.

Edema was reported by 3.2% of patients on rosiglitazone maleate and glimepiride tablets, 3.0% on rosiglitazone alone, and 2.3% on glimepiride alone.

Congestive heart failure was observed in 1 (0.2%) patient treated with rosiglitazone maleate and glimepiride tablets and in 1 (0.4%) patient treated with rosiglitazone monotherapy.

Patients Treated With Rosiglitazone Added to Sulfonylurea Monotherapy and Other Experience With Rosiglitazone or Glimepiride: Trials utilizing rosiglitazone in combination with a sulfonylurea provide support for the use of rosiglitazone maleate and glimepiride tablets. Adverse event data from these trials, in addition to adverse events reported with the use of rosiglitazone and glimepiride therapy, are presented below.

Rosiglitazone: The most common adverse experiences with rosiglitazone monotherapy (≥ 5%) were upper respiratory tract infection, injury, and headache. Overall, the types of adverse experiences reported when rosiglitazone was added to a sulfonylurea were similar to those during monotherapy with rosiglitazone. 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%).

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.

Edema was reported by 4.8% of patients receiving rosiglitazone compared with 1.3% on placebo, and 1.0% on sulfonylurea monotherapy. The reporting rate of edema was higher for rosiglitazone 8 mg added to a sulfonylurea (12.4%) compared with other combinations, with the exception of insulin. Anemia was reported by 1.9% of patients receiving rosiglitazone compared with 0.7% on placebo, 0.6% on sulfonylurea monotherapy, and 2.3% on rosiglitazone in combination with a sulfonylurea. Overall, the types of adverse experiences reported when rosiglitazone was added to a sulfonylurea were similar to those during monotherapy with rosiglitazone.

In 26-week, double-blind, fixed-dose trials, edema was reported with higher frequency in the rosiglitazone plus insulin combination trials (insulin, 5.4%; and rosiglitazone in combination with insulin, 14.7%). 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 *[see Boxed Warning, Warnings and Precautions (5.1)]*.

Long-term Trial of Rosiglitazone as Monotherapy: A 4- to 6-year trial (ADOPT) compared the use of rosiglitazone (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 4** 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 (9.3%, 2.7/100 patient-years) compared with 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 4. 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 as Monotherapy (ADOPT)

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

Long-term Trial of Rosiglitazone as Combination Therapy (RECORD): RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) was a multicenter, randomized, open-label, non-inferiority trial in subjects with type 2 diabetes inadequately controlled on maximum doses of metformin or sulfonylurea (glyburide, gliclazide, or glimepiride) to compare the time to reach the combined cardiovascular endpoint of cardiovascular death or cardiovascular hospitalization between patients randomized to the addition of rosiglitazone versus metformin or sulfonylurea. The trial included patients who have failed metformin or sulfonylurea monotherapy; those who failed metformin (n = 2,222) were randomized to receive either add-on sulfonylurea (n = 1,117) or add-on rosiglitazone (n = 1,105), and those who failed sulfonylurea (n = 2,225) were randomized to receive either add-on rosiglitazone (n = 1,103) or add-on metformin (n = 1,122). Patients were treated to target HbA1c ≤ 7% throughout the trial.

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

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

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

There was an increased incidence of bone fracture for subjects randomized to rosiglitazone in addition to metformin or sulfonylurea compared with those randomized to metformin plus sulfonylurea (8.3% versus 5.3%) *[see Warnings and Precautions (5.8)]*. The majority of fractures were reported in the upper limbs and distal lower limbs. The risk of fracture appeared to be higher in females relative to control (11.5% versus 6.3%), than in males relative to control (5.3% versus 4.3%). Additional data are necessary to determine whether there is an increased risk of fracture in males after a longer period of follow-up.

Glimepiride: Approximately 2,800 patients with type 2 diabetes have been treated with glimepiride in the controlled clinical trials. In these trials, approximately 1,700 patients were treated with glimepiride for at least 1 year.

Table 6 summarizes adverse events, other than hypoglycemia, that were reported in 11 pooled placebo-controlled trials, whether or not considered to be possibly or probably related to study medication. Treatment duration ranged from 13 weeks to 12 months. Terms that are reported represent those that occurred at an incidence of ≥ 5% among glimepiride-treated patients and more commonly than in patients who received placebo.

Table 6. Eleven Pooled Placebo-Controlled Trials Ranging From 13 Weeks to 12 Months: Adverse Events (Excluding Hypoglycemia) Occurring in ≥ 5% of Glimepiride-Treated Patients and at a Greater Incidence Than With Placebo[1]

Preferred Term	Glimepiride N = 745 %	Placebo N = 294 %
Headache	8.2	7.8
Accidental injury[2]	5.8	3.4
Flu syndrome	5.4	4.4
Nausea	5.0	3.4
Dizziness	5.0	2.4

1. Glimepiride doses ranges from 1 to 16 mg administered daily.
2. Insufficient information to determine whether any of the accidental injury events were associated with hypoglycemia.

Hypoglycemia: In a randomized, double-blind, placebo-controlled monotherapy trial of 14 weeks duration, patients already on sulfonylurea therapy underwent a 3-week washout period then were randomized to glimepiride 1 mg, 4 mg, 8 mg or placebo. Patients randomized to glimepiride 4 mg or 8 mg underwent forced-titration from an initial dose of 1 mg to these final doses, as tolerated. The overall incidence of possible hypoglycemia (defined by the presence of at least one symptom that the investigator believed might be related to hypoglycemia; a concurrent glucose measurement was not required) was 4% for glimepiride 1 mg, 17% for glimepiride 4 mg, 16% for glimepiride 8 mg, and 0% for placebo. All of these events were self-treated.

In a randomized, double-blind, placebo-controlled monotherapy trial of 22 weeks duration, patients received a starting dose of either 1 mg glimepiride or placebo daily. The dose of glimepiride was titrated to a target fasting plasma glucose of 90 to 150 mg/dL. Final daily doses of glimepiride were 1, 2, 3, 4, 6, or 8 mg. The overall incidence of possible hypoglycemia (as defined above for the 14-week trial) for glimepiride versus placebo was 19.7% versus 3.2%. All of these events were self-treated.

Weight gain: Glimepiride, like all sulfonylureas, can cause weight gain.

Allergic Reactions: In clinical trials, allergic reactions, such as pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occurred in less than 1% of glimepiride treated patients. These may resolve despite continued treatment with glimepiride. There are postmarketing reports of more serious allergic reactions (e.g., dyspnea, hypotension, shock) *[see Warnings and Precautions (5.9)]*.

6.2 Laboratory Abnormalities

Rosiglitazone: *Hematologic:* Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult patients treated with rosiglitazone (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 or following a dose increase in rosiglitazone. The time course and magnitude of decreases were similar in patients treated with a combination of rosiglitazone and other hypoglycemic agents or monotherapy with rosiglitazone. White blood cell counts also decreased slightly in adult patients treated with rosiglitazone. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with rosiglitazone.

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

Serum Transaminase Levels: In pre-approval clinical trials in 4,598 patients treated with rosiglitazone encompassing approximately 3,600 patient-years of exposure, there was no evidence of drug-induced hepatotoxicity.

In pre-approval controlled trials, 0.2% of patients treated with rosiglitazone had reversible elevations in ALT > 3X the upper limit of normal compared with 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with rosiglitazone were reversible. Hyperbilirubinemia was found in 0.3% of patients treated with rosiglitazone 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 (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).

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

Glimepiride: *Serum Transaminase Levels:* In 11 pooled, placebo-controlled trials of glimepiride, 1.9% of glimepiride-treated patients and 0.8% of placebo-treated patients developed serum ALT > 2X the upper limit of the reference range.

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 and glimepiride tablets or their individual components. 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.

Rosiglitazone: 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, Warnings and Precautions (5.1)]*.

There are postmarketing reports with rosiglitazone 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 of rash, pruritus, urticaria, angioedema, anaphylactic reaction, Stevens-Johnson syndrome *[see Contraindications (4)]*, and new onset or worsening diabetic macular edema with decreased visual acuity *[see Warnings and Precautions (5.7)]*.

Glimepiride:

- Serious hypersensitivity reactions, including anaphylaxis, angioedema, and Stevens-Johnson syndrome *[see Warnings and Precautions (5.9)]*
- Hemolytic anemia in patients with and without G6PD deficiency *[see Warnings and Precautions (5.11)]*
- Impairment of liver function (e.g., with cholestasis and jaundice), as well as hepatitis, which may progress to liver failure
- Porphyria cutanea tarda, photosensitivity reactions, and allergic vasculitis
- Leukopenia, agranulocytosis, aplastic anemia, and pancytopenia
- Thrombocytopenia (including severe cases with platelet count less than 10,000/microliter) and thrombocytopenic purpura
- Hepatic porphyria reactions and disulfiram-like reactions
- Hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH), most often in patients who are on other medications or who have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P450

Rosiglitazone: 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)]*.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is not known. Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 2C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid *[see Clinical Pharmacology (12.4)]*.

Glimepiride: There may be an interaction between glimepiride and inhibitors (e.g., fluconazole) and inducers (e.g., rifampin) of CYP 2C9. Fluconazole may inhibit the metabolism of glimepiride, causing increased plasma concentrations of glimepiride which may lead to hypoglycemia. Rifampin may induce the metabolism of glimepiride, causing decreased plasma concentrations of glimepiride which may lead to worsening glycemic control.

7.2 Drugs Affecting Glucose Metabolism

A number of medications affect glucose metabolism and may require glimepiride dose adjustment and particularly close monitoring for hypoglycemia or worsening glycemic control.

The following are examples of medications that may increase the glucose-lowering effect of sulfonylureas including glimepiride, increasing the susceptibility to and/or intensity of hypoglycemia: oral anti-diabetic medications, pramlintide acetate, insulin, angiotensin converting enzyme (ACE) inhibitors, H2 receptor antagonists, fibrates, propoxyphene, pentoxifylline, somatostatin analogs, anabolic steroids and androgens, cyclophosphamide, phenyramidol, guanethidine, fluconazole, sulfinpyrazone, tetracyclines, clarithromycin, disopyramide, quinolones, and those drugs that are highly protein-bound, such as fluoxetine, nonsteroidal anti-inflammatory drugs, salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, and monoamine oxidase inhibitors. When these medications are administered to a patient receiving rosiglitazone maleate and glimepiride tablets, monitor the patient closely for hypoglycemia. When these medications are withdrawn from a patient receiving rosiglitazone maleate and glimepiride tablets, monitor the patient closely for worsening glycemic control.

The following are examples of medications that may reduce the glucose-lowering effect of sulfonylureas including glimepiride, leading to worsening glycemic control: danazol, glucagon, somatropin, protease inhibitors, atypical antipsychotic medications (e.g., olanzapine and clozapine), barbiturates, diazoxide, laxatives, rifampin, thiazides and other diuretics, corticosteroids, phenothiazines, thyroid hormones, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics (e.g., epinephrine, albuterol, and terbutaline), and isoniazid. When these medications are administered to a patient receiving rosiglitazone maleate and glimepiride tablets, monitor the patient closely for worsening glycemic control. When these medications are withdrawn from a patient receiving rosiglitazone maleate and glimepiride tablets, monitor the patient closely for hypoglycemia.

Beta-blockers, clonidine, and reserpine may lead to either potentiation or weakening of glimepiride's glucose-lowering effect.

Both acute and chronic alcohol intake may potentiate or weaken the glucose-lowering action of glimepiride in an unpredictable fashion.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

7.3 Miconazole

A potential interaction between oral miconazole and sulfonylureas leading to severe hypoglycemia has been reported. Whether this interaction also occurs with other dosage forms of miconazole is not known.

7.4 Concomitant Administration of Colesevelam

Colesevelam can reduce the maximum plasma concentration and total exposure of glimepiride when the two are coadministered. However, absorption is not reduced when glimepiride is administered 4 hours prior to colesevelam. Therefore, rosiglitazone maleate and glimepiride tablets should be administered at least 4 hours prior to colesevelam.

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. Rosiglitazone maleate and glimepiride tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data: There are no adequate and well-controlled trials with rosiglitazone maleate and glimepiride tablets or their individual components in pregnant women. Rosiglitazone has been reported to cross the human placenta and be detectable in fetal tissue. The clinical significance of these findings is unknown.

Animal Studies: No animal studies have been conducted with rosiglitazone maleate and glimepiride tablets. The following data are based on findings in studies performed with rosiglitazone or glimepiride individually.

Rosiglitazone: 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.

Glimepiride: In animal studies there was no increase in congenital anomalies, but an increase in fetal deaths occurred in rats and rabbits at glimepiride doses 50 times (rats) and 0.1 times (rabbits) the maximum recommended human dose (based on body surface area). This fetotoxicity, observed only at doses inducing maternal hypoglycemia, is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride and has been similarly noted with other sulfonylureas.

Nonteratogenic Effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers receiving a sulfonylurea at the time of delivery.

8.2 Labor and Delivery

The effect of rosiglitazone maleate and glimepiride tablets or their components on labor and delivery in humans is unknown.

8.3 Nursing Mothers

No trials have been conducted with rosiglitazone maleate and glimepiride tablets. It is not known whether rosiglitazone or glimepiride is excreted in human milk. Because many drugs are excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue rosiglitazone maleate and glimepiride tablets, taking into account the importance of the drug to the mother.

Rosiglitazone: Drug-related material was detected in milk from lactating rats.

Glimepiride: During pre-and post-natal studies in rats, significant concentrations of glimepiride were present in breast milk and the serum of the pups. Offspring of rats exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride.

8.4 Pediatric Use

Safety and effectiveness of rosiglitazone maleate and glimepiride tablets in pediatric patients have not been established. Rosiglitazone maleate and glimepiride tablets and their components, rosiglitazone and glimepiride, are not indicated for use in pediatric patients.

8.5 Geriatric Use

Rosiglitazone: 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.

Glimepiride: In clinical trials of glimepiride, 1,053 of 3,491 patients (30%) were ≥ 65 years. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

There were no significant differences in glimepiride pharmacokinetics between patients with type 2 diabetes ≤ 65 years (n = 49) and those > 65 years (n = 42) *[see Clinical Pharmacology (12.3)]*.

Glimepiride is substantially excreted by the kidney. Elderly patients are more likely to have renal impairment. In addition, hypoglycemia may be difficult to recognize in the elderly *[see Dosage and Administration (2.4), Warnings and Precautions (5.3)]*. Use caution when initiating rosiglitazone maleate and glimepiride tablets and increasing the dose of rosiglitazone maleate and glimepiride tablets in this patient population.

10 OVERDOSAGE

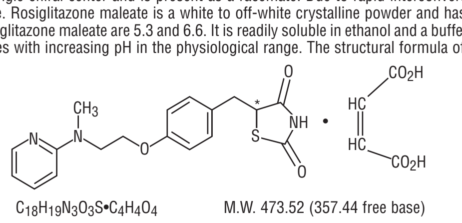
Rosiglitazone: Limited data are available with regard to overdosage in humans. In clinical trials in volunteers, rosiglitazone has been administered at single oral doses of up to 20 mg and was well tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as dictated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

Glimepiride: An overdosage of glimepiride, as with other sulfonylureas, can produce severe hypoglycemia. Mild episodes of hypoglycemia can be treated with oral glucose. Severe hypoglycemic reactions constitute medical emergencies requiring immediate treatment. Severe hypoglycemia with coma, seizure, or neurological impairment can be treated with glucagon or intravenous glucose. Continued observation and additional carbohydrate intake may be necessary because hypoglycemia may recur after apparent clinical recovery *[see Warnings and Precautions (5.3)]*.

11 DESCRIPTION

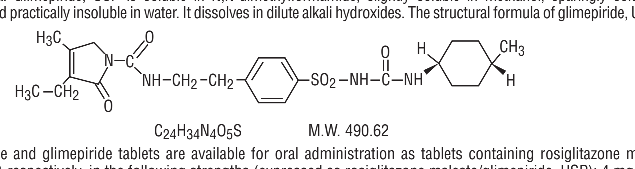
Rosiglitazone maleate and glimepiride tablets contain 2 oral antidiabetic drugs used in the management of type 2 diabetes: rosiglitazone maleate and glimepiride, USP.

Rosiglitazone maleate is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. 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. Rosiglitazone maleate is a white to off-white crystalline powder and has a melting point of about 121°C. The pK_a values of rosiglitazone maleate are 5.3 and 6.6. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range. The structural formula of rosiglitazone maleate is:



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

Glimepiride, USP is an oral antidiabetic drug of the sulfonylurea class. Glimepiride, USP is a white to almost white, odorless powder. Chemically, glimepiride, USP is 1-[[p [2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea. Glimepiride, USP is soluble in N,N-dimethylformamide, slightly soluble in methanol, sparingly soluble in methylene chloride and practically insoluble in water. It dissolves in dilute alkali hydroxides. The structural formula of glimepiride, USP is:



$C_{24}H_{34}N_4O_5S$ M.W. 490.62

Rosiglitazone maleate and glimepiride tablets are available for oral administration as tablets containing rosiglitazone maleate and glimepiride, USP, respectively, in the following strengths (expressed as rosiglitazone maleate/glimepiride, USP): 4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg, 8 mg/2 mg, and 8 mg/4 mg. Each tablet contains the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, talc, and titanium dioxide. Additionally, 4 mg/1 mg contains iron oxide yellow; 4 mg/2 mg tablet contains iron oxide red and iron oxide yellow; 4 mg/4 mg tablet contains iron oxide black, iron oxide red, and iron oxide yellow; 8 mg/2 mg contains FD&C red #40/allura red AC aluminum lake, FD&C blue #2/indigo carmine aluminum lake and FD&C yellow #6/sunset yellow FCF aluminum lake; and 8 mg/4 mg contains FD&C yellow #6 aluminum lake and iron oxide red.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rosiglitazone maleate and glimepiride tablets combine 2 antidiabetic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: Rosiglitazone maleate, a member of the thiazolidinedione class, and glimepiride, a member of the sulfonylurea class. Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas sulfonylureas act primarily by stimulating release of insulin from functioning pancreatic beta cells.

Rosiglitazone: Rosiglitazone 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. Pharmacologic studies in animal models indicate that rosiglitazone improves sensitivity to insulin in muscle and adipose tissue and 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.

Glimepiride: Glimepiride primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Sulfonylureas bind to the sulfonylurea receptor in the pancreatic beta-cell plasma membrane, leading to closure of the ATP-sensitive potassium channel, thereby stimulating the release of insulin.

12.2 Pharmacodynamics

The lipid profiles of rosiglitazone and glimepiride in a clinical trial of patients with inadequate glycemic control on diet and exercise were consistent with the known profile of each monotherapy. Rosiglitazone maleate and glimepiride tablets were associated with increases in HDL and LDL (3% to 4% for each) and decreases in triglycerides (-4%), that were not considered to be clinically meaningful.

The pattern of LDL and HDL changes following therapy with rosiglitazone in patients previously treated with a sulfonylurea was generally similar to those seen with rosiglitazone in monotherapy. Rosiglitazone as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids. The changes in triglycerides during therapy with rosiglitazone were variable and were generally not statistically different from placebo or glyburide controls.

12.3 Pharmacokinetics

In a bioequivalence trial of rosiglitazone maleate and glimepiride tablets 4 mg/4 mg, the area under the curve (AUC) and maximum concentration (C_{max}) of rosiglitazone following a single dose of the combination tablet were bioequivalent to rosiglitazone 4 mg concomitantly administered with glimepiride 4 mg under fasted conditions. The AUC of glimepiride following a single fasted 4 mg/4 mg dose was equivalent to glimepiride concomitantly administered with rosiglitazone, while the C_{max} was 13% lower when administered as the combination tablet (see Table 7).

Table 7. Pharmacokinetic Parameters for Rosiglitazone and Glimepiride (N = 28)

Parameter (Units)	Rosiglitazone Regimen A	Rosiglitazone Regimen B	Glimepiride Regimen A	Glimepiride Regimen B
AUC_{0-inf} (ng.h/mL)	1,259 (833 to 2,060)	1,253 (756 to 2,758)	1,052 (643 to 2,117)	1,101 (648 to 2,555)
AUC_{0-t} (ng.h/mL)	1,231 (810 to 2,019)	1,224 (744 to 2,654)	944 (511 to 1,898)	1,038 (606 to 2,337)
C_{max} (ng/mL)	257 (157 to 352)	251 (77.3 to 434)	151 (63.2 to 345)	173 (70.5 to 329)
$T_{½}$ (h)	3.53 (2.60 to 4.57)	3.54 (2.10 to 5.03)	7.63 (4.42 to 12.4)	5.08 (1.80 to 11.31)
T_{max} (h)	1.00 (0.48 to 3.02)	0.98 (0.48 to 5.97)	3.02 (1.50 to 8.00)	2.53 (1.00 to 8.03)

AUC = area under the curve; C_{max} = maximum concentration; $T_{1/2}$ = terminal half-life; T_{max} = time of maximum concentration.

Regimen A = rosiglitazone maleate and glimepiride tablets 4 mg/4 mg tablet; Regimen B = Concomitant dosing of a rosiglitazone 4-mg tablet AND a glimepiride 4-mg tablet.

Data presented as geometric mean (range), except $T_{1/2}$ which is presented as arithmetic mean (range) and T_{max}, which is presented as median (range).

The rate and extent of absorption of both the rosiglitazone component and glimepiride component of rosiglitazone maleate and glimepiride tablets when taken with food were equivalent to the rate and extent of absorption of rosiglitazone and glimepiride when administered concomitantly as separate tablets with food.

Absorption: The AUC and C_{max} of glimepiride increased in a dose-proportional manner following administration of rosiglitazone maleate and glimepiride tablets 4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg. Administration of rosiglitazone maleate and glimepiride tablets in the fed state resulted in no change in the overall exposure of rosiglitazone; however, the C_{max} of rosiglitazone decreased by 32% compared with the fasted state. There was an increase in both AUC (19%) and C_{max} (55%) of glimepiride in the fed state compared with the fasted state.

Rosiglitazone: The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing. The C_{max} and AUC of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range.

Glimepiride: Studies with single oral doses of glimepiride in healthy subjects and with multiple oral doses in patients with type 2 diabetes showed peak drug concentrations (C_{max}) 2 to 3 hours post-dose. When glimepiride was given with meals, the mean C_{max} and AUC were decreased by 8% and 9%, respectively.

Glimepiride does not accumulate in serum following multiple dosing. The pharmacokinetics of glimepiride does not differ between healthy subjects and patients with type 2 diabetes. Clearance of glimepiride after oral administration does not change over the 1 mg to 8 mg dose range, indicating linear pharmacokinetics.

In healthy subjects, the intra-and inter-individual variabilities of glimepiride pharmacokinetic parameters were 15 to 23% and 24 to 29%, respectively.

Distribution: *Rosiglitazone:* The mean (CV%) oral volume of distribution (V_{ss}/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.

Glimepiride: After intravenous (IV) dosing in healthy subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metabolism and Excretion: *Rosiglitazone:* 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. Following oral or IV 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. The elimination half-life is 3 to 4 hours and is independent of dose.

Glimepiride: Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 is involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M2 is inactive. In animals, M1 possesses about 1/3 of the pharmacological activity of glimepiride, but it is unclear whether M1 results in clinically meaningful effects on blood glucose in humans.

When [^{14}C]glimepiride was given orally to 3 healthy male subjects, approximately 60% of the total radioactivity was recovered in the urine in 7 days. M1 and M2 accounted for 80% to 90% of the radioactivity recovered in the urine. The ratio of M1 to M2 in the urine was approximately 3:2 in two subjects and 4:1 in one subject. Approximately 40% of the total radioactivity was recovered in feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent drug was recovered from urine or feces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite was observed.

Special Populations: No pharmacokinetic data are available for rosiglitazone maleate and glimepiride tablets in the following special populations. Information is provided for the individual components of rosiglitazone maleate and glimepiride tablets.

Gender: Rosiglitazone: Results of the population pharmacokinetics analysis showed that the mean oral clearance of rosiglitazone in female patients (N = 405) was approximately 6% lower compared with male patients of the same body weight (N = 642). Combination therapy with rosiglitazone and sulfonylureas improved glycemic control in both males and females with a greater therapeutic response observed in females. For a given body mass index (BMI), females tend to have a greater fat mass than males. Since the molecular target of rosiglitazone, PPARγ, is expressed in adipose tissues, this differentiating characteristic may account, at least in part, for the greater response to rosiglitazone in combination with sulfonylureas in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.

Glimepiride: There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight.

Geriatric: Rosiglitazone: Results of the population pharmacokinetics analysis (N = 716 < 65 years; N = 331 ≥ 65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone.

Glimepiride: A comparison of glimepiride pharmacokinetics in patients with type 2 diabetes ≤ 65 years and those > 65 years was evaluated in a multiple-dose study using glimepiride 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the 2 age groups. The mean AUC at steady state for the older patients was approximately 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was approximately 11% higher than that for the younger patients *[see Use in Specific Populations (8.5)]*.

Hepatic Impairment: Therapy with rosiglitazone maleate and glimepiride 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 baseline *[see Warnings and Precautions (5.6)]*.

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

Glimepiride: It is unknown whether there is an effect of hepatic impairment on glimepiride pharmacokinetics because the pharmacokinetics of glimepiride has not been adequately evaluated in patients with hepatic impairment.

Obese Patients: Glimepiride: The pharmacokinetics of glimepiride and its metabolites were measured in a single-dose study involving 28 patients with type 2 diabetes who either had normal body weight or were morbidly obese. While the T_{max}, Cl, and Vd of glimepiride in the morbidly obese patients were similar to those in the normal weight group, the morbidly obese had lower C_{max} and AUC than those of normal body weight. The mean C_{max}, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$ values of glimepiride in normal versus morbidly obese patients were 547 ± 218 ng/mL versus 410 ± 124 ng/mL, 3,210 ± 1,030 hours.ng/mL versus 2,820 ± 1,110 hours.ng/mL and 4,000 ± 1,320 hours.ng/mL versus 3,280 ± 1,360 hours.ng/mL, respectively.

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

Glimepiride: No studies have been conducted to assess the effects of race on glimepiride pharmacokinetics, but in placebo-controlled trials of glimepiride in patients with type 2 diabetes, the reduction in HbA1c was comparable in whites (N = 536), blacks (N = 63), and Hispanics (N = 63).

Renal Impairment: Rosiglitazone: 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 with subjects with normal renal function.

Glimepiride: In a single-dose, open-label study, glimepiride 3 mg was administered to patients with mild, moderate, and severe renal impairment as estimated by creatinine clearance (Cl_{cr}): Group I consisted of 5 patients with mild renal impairment (CL_{cr} > 50 mL/min), Group II consisted of 3 patients with moderate renal impairment (CL_{cr} = 20 to 50 mL/min), and Group III consisted of 7 patients with severe renal impairment (CL_{cr} < 20 mL/min). Although glimepiride serum concentrations decreased with decreasing renal function, Group III had a 2.3-fold higher mean AUC for M1 and an 8.6-fold higher mean AUC for M2 compared to corresponding mean AUCs in Group I. The apparent terminal half-life ($T_{½}$) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as a percentage of dose decreased from 44.4% for Group I to 21.9% for Group II and 9.3% for Group III).

Pediatric: No pharmacokinetic data from trials in pediatric subjects are available for rosiglitazone maleate and glimepiride tablets.

Rosiglitazone: 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/h 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.

Glimepiride: The pharmacokinetics of glimepiride (1 mg) were evaluated in a single-dose trial conducted in 30 type 2 diabetic patients (male = 7; female = 23) between ages 10 and 17 years. The mean (±SD) $AUC_{0\text{-}last}$ (339 ± 203 ng.h/mL), C_{max} (102 ± 48 ng/mL), and $t_{½}$ (3.1 ± 1.7 hours) were comparable to historical data from adults ($AUC_{0\text{-}last}$ 315 ± 96 ng.h/mL, C_{max} 103 ± 34 ng/mL, and $t_{½}$ 5.3 ± 4.1 hours).

12.4 Drug-drug Interactions

Single oral doses of glimepiride in 14 healthy adult subjects had no clinically significant effect on the steady-state pharmacokinetics of rosiglitazone. 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.

Rosiglitazone: *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 *[see Drug Interactions (7.1)]*.

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 with 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 with the administration of rosiglitazone (8 mg) alone *[see Drug Interactions (7.1)]*.[1]

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.

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 had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers.

Additional pharmacokinetic trials demonstrated no clinically relevant effect of acarbose, ranitidine, or metformin on the pharmacokinetics of rosiglitazone.

Glimepiride:

Aspirin: In a randomized, double-blind, two-period, crossover study, healthy subjects were given either placebo or aspirin 1 gram three times daily for a total treatment period of 5 days. On Day 4 of each study period, a single 1 mg dose of glimepiride was administered. The glimepiride doses were separated by a 14-day washout period. Coadministration of aspirin and glimepiride resulted in a 34% decrease in the mean glimepiride AUC and a 4% decrease in the mean glimepiride C_{max}.

Colesevelam: Concomitant administration of colesevelam and glimepiride resulted in reductions in glimepiride $AUC_{0\text{-}\infty}$ and C_{max} of 18% and 8%, respectively. When glimepiride was administered 4 hours prior to colesevelam, there was no significant change in glimepiride $AUC_{0\text{-}\infty}$ or C_{max}, -6% and 3%, respectively *[see Dosage and Administration (2.1) and Drug Interactions (7.4)]*.

Cimetidine and Ranitidine: In a randomized, open-label, 3-way, crossover study, healthy subjects received either a single 4 mg dose of glimepiride alone, glimepiride with ranitidine (150 mg twice daily for 4 days; glimepiride was administered on Day 3), or glimepiride with cimetidine (800 mg daily for 4 days; glimepiride was administered on Day 3). Coadministration of cimetidine or ranitidine with a single 4-mg oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride.

Propranolol: In a randomized, double-blind, two-period, crossover study, healthy subjects were given either placebo or propranolol 40 mg three times daily for a total treatment period of 5 days. On Day 4 of each study period, a single 2 mg dose of glimepiride was administered. The glimepiride doses were separated by a 14-day washout period. Concomitant administration of propranolol and glimepiride significantly increased glimepiride C_{max}, AUC, and $T_{½}$ by 23%, 22%, and 15%, respectively, and decreased glimepiride CL/F by 18%. The recovery of M1 and M2 from urine was not changed.

Warfarin: In an open-label, two-way, crossover study, healthy subjects received 4 mg of glimepiride daily for 10 days. Single 25 mg doses of warfarin were administered 6 days before starting glimepiride and on Day 4 of glimepiride administration. The concomitant administration of glimepiride did not alter the pharmacokinetics of R-and S-warfarin enantiomers. No changes were observed in warfarin plasma protein binding. Glimepiride resulted in a statistically significant decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride treatment were 3.3% and 9.9%, respectively, and are unlikely to be clinically relevant.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted with rosiglitazone maleate and glimepiride tablets. The following data are based on findings in studies performed with rosiglitazone or glimepiride alone.

Rosiglitazone: *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 mg/kg/day, 0.3 mg/kg/day, 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 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.

Glimepiride: *Carcinogenesis:* Studies in rats at doses of up to 5,000 parts per million (ppm) in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation that was dose-related and was thought to be the result of chronic pancreatic stimulation. No adenoma formation in mice was observed at a dose of 320 ppm in complete feed, or 46 to 54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose of 8 mg once daily based on surface area.

Mutagenesis: Glimepiride was non-mutagenic in a battery of *in vitro* and *in vivo* mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, and mouse micronucleus test).

Impairment of Fertility: There was no effect of glimepiride on male mouse fertility in animals exposed up to 2,500 mg/kg body weight (> 1,700 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4,000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

13.2 Animal Toxicology and/or Pharmacology

Rosiglitazone: 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 Patients Inadequately Controlled on Diet and Exercise

In a 28-week, randomized, double-blind, clinical trial, 901 patients with type 2 diabetes inadequately controlled on diet and exercise alone (baseline mean fasting plasma glucose [FPG] 211 mg/dL and baseline mean HbA1c 9.1%) were started on rosiglitazone maleate and glimepiride tablets 4 mg/1 mg, rosiglitazone 4 mg, or glimepiride 1 mg. Doses could be increased at 4-week intervals to reach a target mean daily glucose of ≤ 110 mg/dL. Patients who received rosiglitazone maleate and glimepiride tablets were randomized to 1 of 2 titration schemes differing in the maximum total daily dose (4 mg/4 mg or 8 mg/4 mg). The maximum total daily dose was 8 mg for rosiglitazone monotherapy and 4 mg for glimepiride monotherapy. All treatments were administered as a once-daily regimen. Improvements in FPG and HbA1c were observed in patients treated with rosiglitazone maleate and glimepiride tablets compared with either rosiglitazone or glimepiride alone (see Table 8).

Table 8. Glycemic Parameters in a 28-Week Trial of Rosiglitazone Maleate and Glimepiride Tablets in Patients With Type 2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise

Parameter	Glimepiride	Rosiglitazone	Rosiglitazone Maleate and Glimepiride Tablets 4 mg/4 mg	Rosiglitazone Maleate and Glimepiride Tablets 8 mg/4 mg
Mean Final Dose	3.5 mg	7.5 mg	4.0 mg/3.2 mg	6.8 mg/2.9 mg
N	221	227	221	214
FPG (mg/dL) [mean (SD)]				
Baseline	211 (70)	212 (66)	207 (58)	214 (61)
Change from baseline	-42 (66)	-57 (58)	-70 (57)	-80 (57)
Treatment difference between				
– Rosiglitazone Maleate and Glimepiride Tablets and glimepiride	—	—	-30[1]	-37[1]
– Rosiglitazone Maleate and Glimepiride Tablets and rosiglitazone	—	—	-16[1]	-23[1]
% of patients with ≥ 30 mg/dL decrease from baseline	56%	64%	77%	85%
HbA1c (%) [mean (SD)]				
Baseline	9.0 (1.3)	9.1 (1.3)	9.0 (1.3)	9.2 (1.4)
Change from baseline	-1.7 (1.4)	-1.8 (1.5)	-2.4 (1.4)	-2.5 (1.4)
Treatment difference between				
– Rosiglitazone Maleate and Glimepiride Tablets and glimepiride	—	—	-0.6[1]	-0.7[1]
– Rosiglitazone Maleate and Glimepiride Tablets and rosiglitazone	—	—	-0.7[1]	-0.8[1]
% of patients with ≥ 0.7% decrease from baseline	82%	76%	93%	93%
% of patients at HbA1c Target < 7.0%[2]	49%	46%	75%	72%

1. Least squared means, P < 0.0001 compared with monotherapy.
2. Response is related to baseline HbA1c.

Treatment with rosiglitazone maleate and glimepiride tablets resulted in statistically significant improvements in FPG and HbA1c compared with each of the monotherapies. However, when considering choice of therapy for drug-naïve patients, the risk-benefit of initiating monotherapy or dual therapy should be considered. In particular, the risk of hypoglycemia and weight gain with dual therapy should be taken into account *[see Warnings and Precautions (5.3, 5.5), Adverse Reactions (6.1)]*.

14.2 Patients Previously Treated With Sulfonylureas

The safety and efficacy of rosiglitazone added to a sulfonylurea have been studied in clinical trials in patients with type 2 diabetes inadequately controlled on sulfonylureas alone. No clinical trials have been conducted with the fixed-dose combination of rosiglitazone maleate and glimepiride tablets in patients inadequately controlled on a sulfonylurea or who have initially responded to rosiglitazone alone and require additional glycemic control.

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 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 with placebo plus sulfonylurea or further up-titration of the sulfonylurea. **Table 9** shows pooled data for 8 trials in which rosiglitazone added to sulfonylurea was compared with placebo plus sulfonylurea.

Table 9. Glycemic Parameters in 24- to 26- Week Combination Trials of Rosiglitazone Plus Sulfonylurea

Twice-Daily Divided Dosing (5 Trials)	**Sulfonylurea**	**Rosiglitazone 2 mg Twice Daily + Sulfonylurea**	**Sulfonylurea**	**Rosiglitazone 4 mg Twice Daily + Sulfonylurea**
N	397	497	248	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[1]	—	-53[1]
% 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[1]	—	-1.4[1]
% 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	172	173	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[1]	—	-66[1]
% 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[1]	-	-1.4[1]
% of patients with ≥ 0.7% decrease from baseline	11%	36%	20%	68%

1. P < 0.0001 compared with 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 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 plus glipizide compared with 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 with no change on the glipizide arm.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Rosiglitazone maleate and glimepiride tablets are supplied as follows:

4 mg/1 mg strength: yellow, film-coated, standard convex tablet, debossed with “93” on one side of the tablet and with “7643” on the other side of the tablet in bottles of 30 (NDC 0093-7643-56) and 500 (NDC 0093-7643-05).

4 mg/2 mg strength: orange, film-coated, standard convex tablet, debossed with “93” on one side of the tablet and with “7644” on the other side of the tablet in bottles of 30 (NDC 0093-7644-56) and 500 (NDC 0093-7644-05).

4 mg/4 mg strength: pink, film-coated, standard convex tablet, debossed with “93” on one side of the tablet and with “7642” on the other side of the tablet in bottles of 30 (NDC 0093-7642-56) and 500 (NDC 0093-7642-05).

8 mg/2 mg strength: pink, film-coated, standard convex tablet, debossed with “93” on one side of the tablet and with “7700” on the other side of the tablet in bottles of 30 (NDC 0093-7700-56) and 500 (NDC 0093-7700-05).

8 mg/4 mg strength: red, film-coated, standard convex tablet, debossed with “93” on one side of the tablet and with “7702” on the other side of the tablet in bottles of 30 (NDC 0093-7702-56) and 500 (NDC 0093-7702-05).

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

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

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 following:

- Rosiglitazone maleate and glimepiride tablets are not recommended in patients with symptomatic heart failure.
- A meta-analysis of mostly short-term trials suggested an increased risk for myocardial infarction with rosiglitazone compared with placebo. Data from long-term clinical trials of rosiglitazone versus other antidiabetes agents (metformin or sulfonylureas), including a cardiovascular outcome trial (RECORD), observed no difference in overall mortality or in major adverse cardiovascular events (MACE) and its components.
- Rosiglitazone maleate and glimepiride tablets are 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 also in maintaining the efficacy of drug therapy.
- It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin (HbA1c) 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 and glimepiride tablets.
- The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.
- 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 and glimepiride tablets should immediately report these symptoms to their physician.
- Rosiglitazone maleate and glimepiride tablets should be taken with the first meal of the day.
- Therapy with rosiglitazone, 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 and glimepiride tablets. 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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MEDICATION GUIDE

Rosiglitazone Maleate (ROE-si-GLI-ta-zone MAL-ee-ate) and Glimepiride (glye-MEP-ir-ide) Tablets

Read this Medication Guide carefully before you start taking rosiglitazone maleate and glimepiride 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 and glimepiride tablets, ask your doctor or pharmacist.

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

Rosiglitazone maleate and glimepiride tablets may cause serious side effects, including:

New or worse heart failure

- The risk of heart failure may be higher in people who take rosiglitazone maleate and glimepiride tablets with insulin. Most people who take insulin should not also take rosiglitazone maleate and glimepiride tablets.
- Rosiglitazone, one of the two drugs that make up rosiglitazone maleate and glimepiride 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 and glimepiride tablets.
- If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, rosiglitazone maleate and glimepiride 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

Rosiglitazone maleate and glimepiride tablets can have other serious side effects. Be sure to read the section “What are possible side effects of rosiglitazone maleate and glimepiride tablets?”

What are rosiglitazone maleate and glimepiride tablets?

Rosiglitazone maleate and glimepiride tablets contain 2 prescription medicines to treat diabetes, rosiglitazone maleate and glimepiride. Rosiglitazone maleate and glimepiride tablets are used with diet and exercise to treat adults with type 2 (“adult-onset” or “non-insulin dependent”) diabetes mellitus (“high blood sugar”).

Glimepiride can help your body release more of its own insulin. Rosiglitazone can help your body respond better to the insulin made in your body and does not cause your body to make more insulin. These medicines can work together to help control your blood sugar.

Rosiglitazone maleate and glimepiride 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 and glimepiride tablets are safe and effective in children younger than 18 years old.

Who should not take rosiglitazone maleate and glimepiride tablets?

Many people with heart failure should not start taking rosiglitazone maleate and glimepiride tablets. See “What should I tell my doctor before taking rosiglitazone maleate and glimepiride tablets?”

Do not take rosiglitazone maleate and glimepiride tablets if you are allergic to rosiglitazone or glimepiride or any of the ingredients in rosiglitazone maleate and glimepiride tablets. See the end of this leaflet for a complete list of ingredients in rosiglitazone maleate and glimepiride tablets.

Symptoms of a severe allergic reaction with rosiglitazone maleate and glimepiride tablets may include:

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

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

Before starting rosiglitazone maleate and glimepiride 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 and glimepiride tablets, tell your doctor about all of 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 and should not be treated with rosiglitazone maleate and glimepiride tablets.
- **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 and glimepiride tablets and during treatment as needed.
- **had liver problems while taking REZULIN™ (troglitazone), another medicine for diabetes.**
- **have kidney problems.** If people with kidney problems use rosiglitazone maleate and glimepiride tablets, they may need a lower dose of the medication.
- **have glucose 6-phosphate dehydrogenase (G6PD) deficiency.** This condition runs in families. People with G6PD deficiency who take glimepiride (one of the medicines in rosiglitazone maleate and glimepiride tablets) may develop hemolytic anemia (fast breakdown of red blood cells).
- **are pregnant or plan to become pregnant.** It is not known if rosiglitazone maleate and glimepiride 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 and glimepiride tablets may increase your chances of becoming pregnant. Talk to your doctor about birth control choices while taking rosiglitazone maleate and glimepiride tablets. Tell your doctor right away if you become pregnant while taking rosiglitazone maleate and glimepiride tablets.
- **are breastfeeding or planning to breastfeed.** It is not known if rosiglitazone maleate and glimepiride pass into breast milk. You and your doctor should decide if you will take rosiglitazone maleate and glimepiride tablets or breastfeed. You should not do both.

Tell your doctor about all of the medicines you take including prescription and non-prescription medicines, vitamins or herbal supplements. Rosiglitazone maleate and glimepiride 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 all 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 and glimepiride tablets with other medicines.

How should I take rosiglitazone maleate and glimepiride tablets?

- Take rosiglitazone maleate and glimepiride tablets exactly as prescribed. Your doctor may need to change your dose until your blood sugar is better controlled.
- Take rosiglitazone maleate and glimepiride tablets by mouth one time each day with your first main meal.
- It usually takes a few days for rosiglitazone maleate and glimepiride tablets to start lowering your blood sugar. It may take 2 to 3 months to see the full effect on your blood sugar level.
- Rosiglitazone maleate and glimepiride tablets should be taken at least 4 hours before taking colesevelam (WELCHOL).
- If you miss a dose of rosiglitazone maleate and glimepiride 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 and glimepiride tablets, call your doctor or poison control center right away.
- Test your blood sugar regularly as your doctor tells you.
- Your doctor should do blood tests to check your liver before you start rosiglitazone maleate and glimepiride 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 and glimepiride tablets.
- Call your doctor if you get sick, get injured, get an infection, or have surgery. Rosiglitazone maleate and glimepiride tablets may not control your blood sugar levels during these times. Your doctor may need to stop rosiglitazone maleate and glimepiride tablets for a short time and give you insulin to control your blood sugar level.
- 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 and glimepiride tablets.

What are possible side effects of rosiglitazone maleate and glimepiride tablets?

Rosiglitazone maleate and glimepiride 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 and glimepiride tablets?”
- **Heart attack.** Rosiglitazone maleate and glimepiride tablets may increase the risk of a heart attack. Talk to your doctor about what this means to you.

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.

- **Swelling (edema). Rosiglitazone maleate and glimepiride tablets can** cause swelling due to fluid retention. See “What is the most important information I should know about rosiglitazone maleate and glimepiride tablets?”
- **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, drink alcohol, use another medicine that lowers blood sugar, exercise (particularly hard or long), or if you have certain medical problems. Call your doctor if low blood sugar levels are a problem for you.
- **Weight gain.** Rosiglitazone, one of the medicines in rosiglitazone maleate and glimepiride 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 and glimepiride tablets?”
- **Liver problems.** It is important for your liver to be working normally when you take rosiglitazone maleate and glimepiride tablets. Your doctor should do blood tests to check your liver before you start taking rosiglitazone maleate and glimepiride 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, one of the medicines in rosiglitazone maleate and glimepiride 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).**
- **Ovulation** (release of egg from an ovary in women) 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 and glimepiride tablets?”

The most common side effects with rosiglitazone maleate and glimepiride tablets include 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 and glimepiride tablets?

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

Keep rosiglitazone maleate and glimepiride tablets and all medicines out of the reach of children.

General information about rosiglitazone maleate and glimepiride tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use rosiglitazone maleate and glimepiride tablets for a condition for which they were not prescribed. Do not give rosiglitazone maleate and glimepiride 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 and glimepiride tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about rosiglitazone maleate and glimepiride tablets that is written for healthcare professionals. You can also find out more about rosiglitazone maleate and glimepiride tablets by calling 1-888-838-2872.

What are the ingredients in rosiglitazone maleate and glimepiride tablets?

Active Ingredients: rosiglitazone maleate and glimepiride, USP.

Inactive Ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, talc, and titanium dioxide. Additionally, 4 mg/1 mg contains iron oxide yellow; 4 mg/2 mg tablet contains iron oxide red and iron oxide yellow; 4 mg/4 mg tablet contains iron oxide black, iron oxide red, and iron oxide yellow; 8 mg/2 mg contains FD&C red #40/allura red AC aluminum lake, FD&C blue #2/ indigo carmine aluminum lake and FD&C yellow #6/sunset yellow FCF aluminum lake; and 8 mg/4 mg contains FD&C yellow #6 aluminum lake and iron oxide red.

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

4 mg/1 mg strength: yellow, film-coated, standard convex tablet, debossed with “93” on one side of the tablet and with “7643” on the other side of the tablet.

4 mg/2 mg strength: orange, film-coated, standard convex tablet, debossed with “93” on one side of the tablet and with “7644” on the other side of the tablet.

4 mg/4 mg strength: pink, film-coated, standard convex tablet, debossed with “93” on one side of the tablet and with “7642” on the other side of the tablet.

8 mg/2 mg strength: pink, film-coated, standard convex tablet, debossed with “93” on one side of the tablet and with “7700” on the other side of the tablet.

8 mg/4 mg strength: red, film-coated, standard convex tablet, debossed with “93” on one side of the tablet and with “7702” on the other side of the tablet.

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

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Jerusalem, 9777402, Israel

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North Wales, PA 19454

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MEDICATION GUIDE

Rosiglitazone Maleate (ROE-si-GLI-ta-zone MAL-ee-ate) and Glimepiride (glye-MEP-ir-ide) Tablets

Read this Medication Guide carefully before you start taking rosiglitazone maleate and glimepiride 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 and glimepiride tablets, ask your doctor or pharmacist.

What is the most important information I should know about rosiglitazone maleate and glimepiride tablets?
Rosiglitazone maleate and glimepiride tablets may cause serious side effects, including:

New or worse heart failure

- The risk of heart failure may be higher in people who take rosiglitazone maleate and glimepiride tablets with insulin. Most people who take insulin should not also take rosiglitazone maleate and glimepiride tablets.
- Rosiglitazone, one of the two drugs that make up rosiglitazone maleate and glimepiride 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 and glimepiride tablets.
- If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, rosiglitazone maleate and glimepiride 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

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

What are rosiglitazone maleate and glimepiride tablets?
Rosiglitazone maleate and glimepiride tablets contain 2 prescription medicines to treat diabetes, rosiglitazone maleate and glimepiride. Rosiglitazone maleate and glimepiride tablets are used with diet and exercise to treat adults with type 2 ("adult-onset" or "non-insulin dependent") diabetes mellitus ("high blood sugar").

Glimepiride can help your body release more of its own insulin. Rosiglitazone can help your body respond better to the insulin made in your body and does not cause your body to make more insulin. These medicines can work together to help control your blood sugar.

Rosiglitazone maleate and glimepiride 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 and glimepiride tablets are safe and effective in children younger than 18 years old.

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

Do not take rosiglitazone maleate and glimepiride tablets if you are allergic to rosiglitazone or glimepiride or any of the ingredients in rosiglitazone maleate and glimepiride tablets. See the end of this leaflet for a complete list of ingredients in rosiglitazone maleate and glimepiride tablets.

Symptoms of a severe allergic reaction with rosiglitazone maleate and glimepiride tablets may include:

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

What should I tell my doctor before taking rosiglitazone maleate and glimepiride tablets?
Before starting rosiglitazone maleate and glimepiride 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 and glimepiride tablets, tell your doctor about all of 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 and should not be treated with rosiglitazone maleate and glimepiride tablets.
- **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 and glimepiride tablets and during treatment as needed.
- **had liver problems while taking REZULIN™ (troglitazone), another medicine for diabetes.**
- **have kidney problems.** If people with kidney problems use rosiglitazone maleate and glimepiride tablets, they may need a lower dose of the medication.
- **have glucose 6-phosphate dehydrogenase (G6PD) deficiency.** This condition runs in families. People with G6PD deficiency who take glimepiride (one of the medicines in rosiglitazone maleate and glimepiride tablets) may develop hemolytic anemia (fast breakdown of red blood cells).
- **are pregnant or plan to become pregnant.** It is not known if rosiglitazone maleate and glimepiride 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 and glimepiride tablets may increase your chances of becoming pregnant. Talk to your doctor about birth control choices while taking rosiglitazone maleate and glimepiride tablets. Tell your doctor right away if you become pregnant while taking rosiglitazone maleate and glimepiride tablets.
- **are breastfeeding or planning to breastfeed.** It is not known if rosiglitazone maleate and glimepiride pass into breast milk. You and your doctor should decide if you will take rosiglitazone maleate and glimepiride tablets or breastfeed. You should not do both.

Tell your doctor about all of the medicines you take including prescription and non-prescription medicines, vitamins or herbal supplements. Rosiglitazone maleate and glimepiride 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 all 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 and glimepiride tablets with other medicines.

How should I take rosiglitazone maleate and glimepiride tablets?

- Take rosiglitazone maleate and glimepiride tablets exactly as prescribed. Your doctor may need to change your dose until your blood sugar is better controlled.
- Take rosiglitazone maleate and glimepiride tablets by mouth one time each day with your first main meal.
- It usually takes a few days for rosiglitazone maleate and glimepiride tablets to start lowering your blood sugar. It may take 2 to 3 months to see the full effect on your blood sugar level.
- Rosiglitazone maleate and glimepiride tablets should be taken at least 4 hours before taking colesevelam (WELCHOL).
- If you miss a dose of rosiglitazone maleate and glimepiride 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 and glimepiride tablets, call your doctor or poison control center right away.
- Test your blood sugar regularly as your doctor tells you.
- Your doctor should do blood tests to check your liver before you start rosiglitazone maleate and glimepiride 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 and glimepiride tablets.
- Call your doctor if you get sick, get injured, get an infection, or have surgery. Rosiglitazone maleate and glimepiride tablets may not control your blood sugar levels during these times. Your doctor may need to stop rosiglitazone maleate and glimepiride tablets for a short time and give you insulin to control your blood sugar level.
- 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 and glimepiride tablets.

What are possible side effects of rosiglitazone maleate and glimepiride tablets?
Rosiglitazone maleate and glimepiride 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 and glimepiride tablets?"
- **Heart attack.** Rosiglitazone maleate and glimepiride tablets may increase the risk of a heart attack. Talk to your doctor about what this means to you.

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.

- **Swelling (edema). Rosiglitazone maleate and glimepiride tablets can** cause swelling due to fluid retention. See "What is the most important information I should know about rosiglitazone maleate and glimepiride tablets?"
- **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, drink alcohol, use another medicine that lowers blood sugar, exercise (particularly hard or long), or if you have certain medical problems. Call your doctor if low blood sugar levels are a problem for you.
- **Weight gain.** Rosiglitazone, one of the medicines in rosiglitazone maleate and glimepiride 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 and glimepiride tablets?"
- **Liver problems.** It is important for your liver to be working normally when you take rosiglitazone maleate and glimepiride tablets. Your doctor should do blood tests to check your liver before you start taking rosiglitazone maleate and glimepiride 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
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  - dark urine
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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, one of the medicines in rosiglitazone maleate and glimepiride 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).**
- **Ovulation** (release of egg from an ovary in women) 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 and glimepiride tablets?"

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What are the ingredients in rosiglitazone maleate and glimepiride tablets?
Active Ingredients: rosiglitazone maleate and glimepiride, USP.

Inactive Ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, talc, and titanium dioxide. Additionally, 4 mg/1 mg contains iron oxide yellow; 4 mg/2 mg tablet contains iron oxide red and iron oxide yellow; 4 mg/4 mg tablet contains iron oxide black, iron oxide red, and iron oxide yellow; 8 mg/2 mg contains FD&C red #40/allura red AC aluminum lake, FD&C blue #2/indigo carmine aluminum lake and FD&C yellow #6/sunset yellow FCF aluminum lake; and 8 mg/4 mg contains FD&C yellow #6 aluminum lake and iron oxide red.

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4 mg/1 mg strength: yellow, film-coated, standard convex tablet, debossed with "93" on one side of the tablet and with "7643" on the other side of the tablet.

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4 mg/4 mg strength: pink, film-coated, standard convex tablet, debossed with "93" on one side of the tablet and with "7642" on the other side of the tablet.

8 mg/2 mg strength: pink, film-coated, standard convex tablet, debossed with "93" on one side of the tablet and with "7700" on the other side of the tablet.

8 mg/4 mg strength: red, film-coated, standard convex tablet, debossed with "93" on one side of the tablet and with "7702" on the other side of the tablet.

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