

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

Distribution: Rosiglitazone: The mean (CV%) oral volume of distribution (V_dF) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 98% bound to plasma proteins, primarily albumin. **Excretion:** Metformin: The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg metformin averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules, the plasma half-life of metformin is approximately 4 hours and are reached within 24 to 48 hours and are generally < 1 mg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 mg/mL, even at maximum doses.

Metabolism and Excretion: Rosiglitazone: Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism are N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All 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 CYPchrome P450 (CYP) isoenzyme C2C8, with CYP2C9 contributing as a minor pathway. Following oral or intravenous administration of [¹⁴C]rosiglitazone maleate, approximately 6% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [¹⁴C]labeled material ranged from 103 to 153 hours. The elimination half-life is 3 to 4 hours and is independent of dose.

Metabolism and Excretion: Metformin: Intravenous single-dose trials in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of elimination. Following a single oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.5 hours, suggesting that the erythrocyte mass may be a compartment of distribution. **Special Populations:** Renal Impairment: In subjects with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance. [See **Warnings and Precautions (5.1)** and **Contraindications (4.1)**.] Hepatic Impairment: Limited data indicate that 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-∞} 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.

Therapy with rosiglitazone maleate and metformin hydrochloride 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)**]. No pharmacokinetic trials of metformin have been conducted in subjects with hepatic insufficiency.

Geriatric: Results of the population pharmacokinetics analysis (N = 716 & 65 years; N = 331 > 65 years) showed that age did not significantly affect the pharmacokinetics of rosiglitazone. However, limited data from the pharmacokinetic trials of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function [See *Use in Specific Populations (8.5)*, *GLUCOPHAGE prescribing information*]. Metformin treatment and therefore treatment with rosiglitazone maleate and metformin hydrochloride tablets should not be initiated in patients > 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced [See *Dosage and Administration (2)*, *Warnings and Precautions (5.1)*]. Gender: Results of the population pharmacokinetics analysis showed that the mean oral clearance of rosiglitazone in female patients (N = 405) was approximately 6% lower compared with male patients of the same body weight (N = 642). In rosiglitazone and metformin combination trials, efficacy was demonstrated with no gender differences in glycemic response.

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

Race: 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.

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

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

12.4 Drug-Drug Interactions

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, C2C9. [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.

Gentamicin: Concomitant administration of gentamicin (600 mg twice daily), an inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone AUC_{0-∞} 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 gentamicin is introduced. [See *Drug Interactions (7.1)*.] **Ritampin:** Ritampin administration (600 mg once a day), an inducer of CYP2C8, for 6 days is reported to decrease rosiglitazone AUC_{0-∞} by 66%, compared with the administration of rosiglitazone (6 mg) alone. [See *Drug Interactions (7.1)*.]

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

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

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

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

In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when coadministered in single-dose interactions. The mechanism of interaction between metformin and these drugs is not known.

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

13.1 NONCLINICAL TOXICOLOGY

13.1.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted with rosiglitazone maleate and metformin hydrochloride. The following data are based on findings in studies performed with rosiglitazone or metformin individually.

Rosiglitazone: 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 of the rosiglitazone component of rosiglitazone maleate and metformin hydrochloride). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05, 0.5, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of rosiglitazone maleate and metformin hydrochloride for male and female rats, respectively).

Metformin: 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 of the metformin component of rosiglitazone maleate and metformin hydrochloride, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of rosiglitazone maleate and metformin hydrochloride). 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.

maternal performance or pregnancy incidence in females (approximately 68 times human AUC at the maximum recommended daily dose of rosiglitazone). In monkeys, rosiglitazone (0.6 and 4.8 mg/kg/day, approximately 3 and 15 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of rosiglitazone maleate and metformin hydrochloride, respectively) diminished the follicular phase 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 decreased synthesis of ovarian steroids.

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

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

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

13.2 Animal Toxicology and/or Pharmacology

Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of rosiglitazone maleate and metformin hydrochloride, respectively). Effects in juvenile rats were consistent with those seen in adult rats. In juvenile rats, the incidence of myocardial 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 who Have Inadequate Glycemic Control on Diet and Exercise In a 32 week, randomized, double-blind clinical trial, 468 patients with type 2 diabetes mellitus inadequately controlled on diet and exercise alone (mean baseline FPG 198 mg/dL and mean baseline HbA1c 8.8%) were randomized to rosiglitazone maleate and metformin hydrochloride tablets or metformin hydrochloride tablets alone. Doses were increased at 4 week intervals up to a maximum of 8 mg/2,000 mg for rosiglitazone maleate and metformin hydrochloride, 8 mg for rosiglitazone, and 2,000 mg for metformin to reach a target mean daily glucose of < 110 mg/dL. Following the initial dosage level, rosiglitazone maleate and metformin hydrochloride, rosiglitazone, and metformin were all administered as twice-daily regimens. Statistically significant improvements in FPG and HbA1c were observed in patients treated with rosiglitazone maleate and metformin hydrochloride compared with either rosiglitazone or metformin alone (see **Table 10**). However, when considering the choice of therapy for drug-naïve patients, the risk-benefit of initiating monotherapy or dual therapy should be considered.

Table 10. Glycemic Parameters in a 32 Week Trial of Rosiglitazone Maleate and Metformin Hydrochloride in Patients With Type 2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise

Parameter	Rosiglitazone Maleate and Metformin Hydrochloride	Rosiglitazone	Metformin
Mean Final Dose	7.2 mg/1,799 mg	7.7 mg	1,847 mg
	152	155	150
FPG (mg/dL)			
Baseline (mean)	201	194	199
Change from baseline (mean)	-74	-44	-51
Difference between rosiglitazone maleate and metformin hydrochloride tablets and metformin hydrochloride tablets and monotherapy (adjusted mean)	-27	-22	-25a
% of patients with > 30 mg/dL decrease from baseline	86%	68%	64%
HbA1c (%)			
Baseline (mean)	8.9%	8.8%	8.8%
Change from baseline (mean)	-2.3%	-1.6%	-1.8%
Difference between rosiglitazone maleate and metformin hydrochloride tablets and monotherapy (adjusted mean)	-0.6a	-0.4a	
% of patients with HbA1c ≤ 0.7% decrease from baseline	92%	79%	84%
% of Patients with HbA1c < 7.0%	77%	58%	57%

a P < 0.001, rosiglitazone maleate and metformin hydrochloride compared with rosiglitazone or metformin.

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

14.2 Patients Previously Treated With Metformin

Rosiglitazone maleate and metformin hydrochloride was not studied in patients previously treated with metformin monotherapy; however, the combination of rosiglitazone and metformin was compared with rosiglitazone and metformin monotherapies in clinical trials. Bioequivalence between rosiglitazone maleate and metformin hydrochloride and coadministered rosiglitazone tablets and metformin tablets has been demonstrated [See *Clinical Pharmacology (12.3)*].

In one trial of 607 patients with type 2 diabetes participated in two 26-week, randomized, double-blind, placebo-active-controlled trials designed to assess the efficacy of rosiglitazone in combination with metformin. Rosiglitazone, administered in either once-daily or twice-daily dosing regimens, was added to the therapy of patients who were inadequately controlled on 2.5 grams/day of metformin.

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

Table 11. Glycemic Parameters in a 26 Week Trial of Rosiglitazone Added to Metformin Therapy				
Parameter	Metformin	Rosiglitazone 4 mg Once Daily + Metformin	Rosiglitazone 8 mg Once Daily + Metformin	
N	113	116	110	
FPG (mg/dL)				
Baseline (mean)	214	215	220	
Change from baseline (mean)	6	-33	-48	
Difference from metformin alone (adjusted mean)		-40a	-53a	
% of patients with >30 mg/dL decrease from baseline	20%	45%	61%	
HbA1c (%)				
Baseline (mean)	8.6	8.9	8.9	
Change from baseline (mean)	0.5	-0.6	-0.8	
Difference from metformin alone (adjusted mean)		-1.0a	-1.2a	
% of patients with HbA1c ≤ 0.7% decrease from baseline	11%	45%	52%	

a P < 0.0001 compared with metformin.

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

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Rosiglitazone maleate and metformin hydrochloride tablets are available as follows: 1 mg/500 mg – yellow, film-coated, modified oval-shaped tablets, debossed with “93” on one side and “7530” on the other side of the tablet, in bottles of 60 and 100. 2 mg/500 mg – light-pink, film-coated, modified oval-shaped tablets, debossed with “93” on one side and “7531” on the other side of the tablet, in bottles of 60, 100, and 500. 4 mg/500 mg – orange, film-coated, modified oval-shaped tablets, debossed with “93” on one side and “7532” on the other side of the tablet, in bottles of 60, 100, and 500.

2 mg/1,000 mg – yellow, film-coated, modified oval-shaped tablets, debossed with “93” on one side and “7533” on the other side of the tablet, in bottles of 60 and 100.

4 mg/1,000 mg – pink, film-coated, modified oval-shaped tablets, debossed with “93” on one side and “7534” on the other side of the tablet, in bottles of 60 and 100.

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:

• The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the WARNINGS and PRECAUTIONS sections, should be explained to patients. Patients should be advised to discontinue rosiglitazone maleate and metformin hydrochloride tablets immediately and to promptly notify their health practitioner if: unexplained hyperventilation, myalgia, malaise, unusual, common, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of rosiglitazone maleate and metformin hydrochloride tablets, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

• Avoid excessive alcohol intake, either acute or chronic, while receiving rosiglitazone maleate and metformin hydrochloride tablets. Excessive alcohol consumption may increase the risk of lactic acidosis.

• Rosiglitazone maleate and metformin hydrochloride tablets are not recommended for 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 antidiabetic agents are inconclusive, 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 metformin hydrochloride 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, glycosylated hemoglobin (HbA1c), renal function, and hematologic parameters 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 metformin hydrochloride tablets.

• Blood will be drawn to check the 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 metformin hydrochloride tablets should immediately report these symptoms to their physician. Therapy with rosiglitazone maleate and metformin hydrochloride tablets, 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 metformin hydrochloride 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

(roh-zee-GLIT-ah-zohn MAL-ee-ate) AND

METFORMIN HYDROCHLORIDE

(met-FORE-min hye-droe-KLOR-ide)TABLETS

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

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

Rosiglitazone maleate and metformin hydrochloride 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 metformin hydrochloride tablets with insulin. Most people who take insulin should not also take rosiglitazone maleate and metformin hydrochloride tablets.

• Rosiglitazone, one of the medicines in rosiglitazone maleate and metformin hydrochloride 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 metformin hydrochloride 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 metformin hydrochloride 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

Lactic acidosis

Metformin, one of the medicines in rosiglitazone maleate and metformin hydrochloride tablets, can cause a rare but serious condition called lactic acidosis (a build-up of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Most people who have had lactic acidosis with metformin have other things that, combined with the metformin, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with rosiglitazone maleate and metformin hydrochloride tablets if you:

- have kidney problems or your kidneys are affected by certain X-ray tests that use injectable dye. People with kidney problems should not take rosiglitazone maleate and metformin hydrochloride tablets.
- have liver problems

• drink alcohol very often, or drink a lot of alcohol in short-term “binge” drinking

- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- have surgery
- have a heart attack, severe infection, or stroke
- are 80 years of age or older, and your kidneys are not working properly

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop your rosiglitazone maleate and metformin hydrochloride tablets for a while if you have any of these things.

Lactic acidosis can be hard to diagnose early, because the early symptoms could seem like the symptoms of many other health problems besides lactic acidosis. You should call your doctor right away if you get the following symptoms, which could be signs of lactic acidosis:

- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have stomach pains
- you have trouble breathing
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat

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

What are rosiglitazone maleate and metformin hydrochloride tablets?

Rosiglitazone maleate and metformin hydrochloride tablets contains two prescription medicines for treating diabetes, rosiglitazone maleate (AVANDIA®) and metformin hydrochloride. rosiglitazone maleate and metformin hydrochloride tablets are used, with diet and exercise, to treat adults with type 2 (“adult-onset” or “non-insulin dependent”) diabetes (“high blood sugar”). Metformin works mainly by decreasing the production of sugar by your liver. Rosiglitazone helps your body respond better to its natural insulin and does not cause your body to make more insulin. These medicines work together to help control your blood sugar. Rosiglitazone maleate and metformin hydrochloride tablets may be used alone or with other diabetes medicines.

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

Who should not take rosiglitazone maleate and metformin hydrochloride tablets? Do not take rosiglitazone maleate and metformin hydrochloride tablets if you:

- have kidney problems. Before you take rosiglitazone maleate and metformin hydrochloride tablets and while you take it, your doctor should test your blood to check for signs of kidney problems.
- have a condition known as metabolic

- drink alcohol very often, or drink a lot of alcohol in short-term “binge” drinking
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- have surgery
- have a heart attack, severe infection, or stroke
- are 80 years of age or older, and your kidneys are not working properly

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop your rosiglitazone maleate and metformin hydrochloride tablets for a while if you have any of these things.

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- have kidney problems. Before you take rosiglitazone maleate and metformin hydrochloride tablets and while you take it, your doctor should test your blood to check for signs of kidney problems.
- have a condition known as metabolic acidosis, including diabetic ketoacidosis.
- are going to have an X-ray procedure with an injection of dyes (contrast agents) in your vein with a needle. Talk to your doctor about when to stop rosiglitazone maleate and metformin hydrochloride tablets and when to start it again.

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

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

Symptoms of a severe allergic reaction with rosiglitazone maleate and metformin hydrochloride 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

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

Before starting rosiglitazone maleate and metformin hydrochloride 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 metformin hydrochloride tablets, tell your doctor about all of your medical conditions, including if you:

- have heart problems or heart failure.**
- have kidney problems.**
- have type 1 (“juvenile”) diabetes or had diabetic ketoacidosis.** These conditions should be treated with insulin.
- are going to have dye injected into a vein for an X-ray, CAT scan, heart study, or other type of scanning.**
- drink a lot of alcohol** (all the time or short binge drinking).
- develop a serious condition such as a heart attack, severe infection, or a stroke.**
- are 80 years old or older.** People who are older than 80 years should not take rosiglitazone maleate and metformin hydrochloride tablets unless their kidney function is checked and it is normal.
- 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 metformin hydrochloride tablets and during treatment as needed.
- had liver problems while taking REZULIN™** (troglitazone), another medicine for diabetes.
- are pregnant or plan to become pregnant.** It is not known if rosiglitazone maleate and metformin hydrochloride 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 metformin hydrochloride tablets may increase your chances of becoming pregnant. Talk to your doctor about birth control choices while taking rosiglitazone maleate and metformin hydrochloride tablets. Tell your doctor right away if you become pregnant while taking rosiglitazone maleate and metformin hydrochloride tablets.

- are breastfeeding or planning to breastfeed.** It is not known if rosiglitazone maleate and metformin hydrochloride pass into breast milk. You and your doctor should decide if you will take rosiglitazone maleate and metformin hydrochloride 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 metformin hydrochloride 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. Your doctor may need to change your dose of rosiglitazone maleate and metformin hydrochloride tablets or your other medicines. 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 metformin hydrochloride tablets with other medicines.

How should I take rosiglitazone maleate and metformin hydrochloride tablets?

- Take rosiglitazone maleate and metformin hydrochloride tablets exactly as prescribed. Your doctor may need to change your dose until your blood sugar is better controlled.
- Rosiglitazone maleate and metformin hydrochloride tablets should be taken by mouth and with meals.
- Rosiglitazone maleate and metformin hydrochloride tablets may be prescribed alone or with other diabetes medicines. This will depend on how well your blood sugar is controlled.
- It can take 2 weeks for rosiglitazone maleate and metformin hydrochloride tablets to start lowering your blood sugar. It may take 2 to 3 months to see the full effect on your blood sugar level.
- If you miss a dose of rosiglitazone maleate and metformin hydrochloride 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 metformin hydrochloride tablets, call your doctor or poison control center right away.
- Test your blood sugar regularly as your doctor tells you.

- Diet and exercise can help your body use its blood sugar better. It is important to stay on your recommended diet, lose extra weight, and get regular exercise while taking rosiglitazone maleate and metformin hydrochloride tablets.
- Your doctor should do blood tests to check your liver and kidneys before you start rosiglitazone maleate and metformin hydrochloride 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 metformin hydrochloride tablets.

There may be times when you will need to stop taking rosiglitazone maleate and metformin hydrochloride tablets for a short time. Tell your doctor if you:

- are sick with severe vomiting, diarrhea or fever, or if you drink a much lower amount of liquid than normal.
- are going to have dye injected into a vein for an X-ray, CAT scan, heart study or other type of scanning.
- plan to have surgery.

What should I avoid while taking rosiglitazone maleate and metformin hydrochloride tablets?

Do not drink a lot of alcohol while taking rosiglitazone maleate and metformin hydrochloride tablets. This means you should not “binge drink”, and you should not drink a lot of alcohol on a regular basis. Drinking a lot of alcohol can increase the chance of getting lactic acidosis.

What are possible side effects of rosiglitazone maleate and metformin hydrochloride tablets?

Rosiglitazone maleate and metformin hydrochloride 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 metformin hydrochloride tablets?”
- Heart attack.** Rosiglitazone maleate and metformin hydrochloride 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 metformin hydrochloride tablets can cause swelling due to fluid retention. See “What is the most important information I should know about rosiglitazone maleate and metformin hydrochloride tablets?”
- Weight gain.** Rosiglitazone, one of the medicines in rosiglitazone maleate and metformin hydrochloride tablets, can cause weight gain that may be due to fluid retention or extra body fat. Metformin, the other medicine in rosiglitazone maleate and metformin hydrochloride tablets, can cause weight loss. There is little change in weight with rosiglitazone maleate and metformin hydrochloride tablets. 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 metformin hydrochloride tablets?”
- Liver problems.** It is important for your liver to be working normally when you take rosiglitazone maleate and metformin hydrochloride tablets. Your doctor should do blood tests to check your liver before you start taking rosiglitazone maleate and metformin hydrochloride tablets and during treatment as needed. Call your doctor right away if you have unexplained symptoms such as:

- nausea and 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 metformin hydrochloride tablets.

- Fractures (broken bones),** usually in the hand, upper arm, or foot. Talk to your doctor for advice on how to keep your bones healthy.

- Low red blood cell count (anemia).**

- Low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness, or hunger may mean that your blood sugar is too low. This can happen if you skip meals, if you use another medicine that lowers blood sugar, or if you have certain medical problems. Call your doctor if low blood sugar levels are a problem for you.

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

Common side effects of rosiglitazone maleate and metformin hydrochloride tablets include:

- Diarrhea, nausea, and upset stomach.** These side effects usually happen during the first few weeks of treatment. Taking rosiglitazone maleate and metformin hydrochloride tablets with food can help lessen these side effects. If you have unusual or unexpected stomach problems, talk with your doctor. Stomach problems that start up later during treatment with rosiglitazone maleate and metformin hydrochloride tablets may be a sign of something more serious and should be discussed with your doctor.

- Cold-like symptoms**

- Headache**
- Joint aches**
- Dizziness**

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 metformin hydrochloride tablets?

- Store rosiglitazone maleate and metformin hydrochloride tablets at room temperature, 59°F to 86°F (15°C to 30°C).
- Keep rosiglitazone maleate and metformin hydrochloride tablets in the container it comes in. Keep the container closed tightly.
- Safely, throw away rosiglitazone maleate and metformin hydrochloride tablets that is out of date or no longer needed.

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

General information about rosiglitazone maleate and metformin hydrochloride tablets

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

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

What are the ingredients in rosiglitazone maleate and metformin hydrochloride tablets?

Active Ingredients: rosiglitazone maleate and metformin hydrochloride

Inactive Ingredients: colloidal silicon dioxide, corn starch, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, and titanium dioxide. Additionally, 1 mg/500 mg tablets contain iron oxide yellow, 2 mg/500 mg tablets contain iron oxide red, 4 mg/500 mg tablets contain iron oxide red and iron oxide yellow, 2 mg/1,000 mg tablets contain iron oxide yellow, 4 mg/1,000 mg tablets contain iron oxide black and iron oxide red.

Always check to make sure that the medicine you are taking is the correct one. Rosiglitazone maleate and metformin hydrochloride tablets are oval and look like this:

- 1 mg/500 mg – yellow, film-coated, modified oval-shaped tablets, debossed with “93” on one side and “7530” on the other side of the tablet.
- 2 mg/500 mg – light-pink, film-coated, modified oval-shaped tablets, debossed with “93” on one side and “7531” on the other side of the tablet.
- 4 mg/500 mg – orange, film-coated, modified oval-shaped tablets, debossed with “93” on one side and “7532” on the other side of the tablet.

- 2 mg/1,000 mg – yellow, film-coated, modified oval-shaped tablets, debossed with “93” on one side and “7533” on the other side of the tablet.

- 4 mg/1,000 mg – pink, film-coated, modified oval-shaped tablets, debossed with “93” on one side and “7534” 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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