PRODUCT MONOGRAPH

# PrTEVA-ROSIGLITAZONE

rosiglitazone (as rosiglitazone maleate)

2 mg, 4 mg and 8 mg Tablets

Professed Standard

Antidiabetic Agent

Teva Canada Limited.
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**TEVA-ROSIGLITAZONE**

rosiglitazone as rosiglitazone maleate

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Oral | Tablet / 2 mg, 4 mg and 8 mg | Hydroxyl propyl methyl cellulose, iron oxide red, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, talc, titanium dioxide and triacetin.<br><br>In addition each strength contains the following ingredients: **2 mg:** FD & C Blue #2/ Indigo Carmne Aluminum Lake, **4 mg:** iron oxide yellow and **8 mg:** iron oxide yellow and iron oxide black. |

### INDICATIONS AND CLINICAL USE

TEVA-ROSIGLITAZONE (rosiglitazone maleate) is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus for whom all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance. (See **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions Box and Cardiovascular**).

Prior to prescribing TEVA-ROSIGLITAZONE physicians must:

- Document the eligibility of patients to meet the above criteria;
- Counsel each patient on the risks and benefits of TEVA-ROSIGLITAZONE including the cardiovascular risks; and
- Obtain the patient's written informed consent to take the drug.

In combination therapy, TEVA-ROSIGLITAZONE is only indicated with metformin OR a sulfonylurea.

Caloric restriction, weight loss, and exercise improve insulin sensitivity and are essential for the proper treatment of a diabetic patient. These measures are important not only in the primary treatment of type 2 diabetes, but also in maintaining the efficacy of drug therapy. Prior to initiation of therapy with TEVA-ROSIGLITAZONE, secondary causes of poor glycemic control (e.g. infection) should be investigated and treated.

**Geriatrics (≥ 65 years of age):**
Evidence from clinical studies and experience suggest that use in the geriatric population may be associated with differences in safety See WARNINGS & PRECAUTIONS, Cardiovascular.

**Pediatrics (< 18 years of age):**
The safety and effectiveness of rosiglitazone have not been established in patients younger than 18 years of age. Furthermore, thiazoledinediones promote the maturation of preadipocytes and have been associated with weight gain. Therefore, TEVA-ROSIGLITAZONE is not indicated in patients younger than 18 years of age. See WARNINGS AND PRECAUTIONS, Special Populations.

## CONTRAINDICATIONS

TEVA-ROSIGLITAZONE is contraindicated in:

- Patients with New York Heart Association (NYHA) Class I to IV heart failure.
- Patients with known hypersensitivity to this product or any of its ingredients.
- Patients with serious hepatic impairment (see WARNINGS AND PRECAUTIONS).
- Pregnancy. Insulin is recommended during pregnancy to control blood glucose levels. Oral antidiabetic agents should not be given (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

- TEVA-ROSIGLITAZONE like other thiazolidinediones, can cause fluid retention and congestive heart failure (See **Cardiovascular** below).

- TEVA-ROSIGLITAZONE may be associated with an increased risk of cardiac ischemia. TEVA-ROSIGLITAZONE **is not recommended in patients with a history of ischemic heart disease, particularly those with myocardial ischemic symptoms.** (See **Cardiovascular** below).

- TEVA-ROSIGLITAZONE should be used only when all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance (See **Cardiovascular** below).

### General

Rosiglitazone maleate is active only in the presence of insulin due to its mechanism of action. Therefore, TEVA-ROSIGLITAZONE should not be used in the treatment of type 1 diabetes or for the treatment of diabetic ketoacidosis.

For safety reasons, the use of TEVA-ROSIGLITAZONE in combination with insulin is not indicated (see CLINICAL TRIALS).

The use of TEVA-ROSIGLITAZONE in combination with metformin AND a sulfonylurea (triple therapy) is not indicated. An increase in reporting of fluid retention related events (including congestive heart failure) has been seen in patients receiving rosiglitazone in combination with metformin AND a sulfonylurea.

Close monitoring of glycemic control and rosiglitazone dose adjustment may be needed when rosiglitazone is co-administered with CYP2C8 inhibitors or inducers (see DRUG INTERACTIONS).

### Carcinogenesis and Mutagenesis

See TOXICOLOGY.

### Cardiovascular

Rosiglitazone maleate can cause fluid retention, congestive heart failure, and may be associated with an increased risk of cardiac ischemia. Some studies have reported an increased cardiovascular risk with rosiglitazone maleate compared to another member of the thiazolidinedione class, pioglitazone. **TEVA-ROSIGLITAZONE should be used only when all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance.**
**Congestive heart failure:** Thiazolidinediones, like rosiglitazone maleate, alone or in combination with other antidiabetic agents, can cause fluid retention, which can exacerbate or lead to congestive heart failure. The fluid retention may very rarely present as rapid and excessive weight gain. All patients should be monitored for signs and symptoms of adverse reactions relating to fluid retention and heart failure. In particular, patients who are at risk for

heart failure including those receiving concurrent therapy which increases insulin levels (i.e. sulfonylureas), should be closely monitored. (See ADVERSE REACTIONS). An increase in reporting of fluid retention related events including congestive heart failure has been seen in patients receiving rosiglitazone in combination with metformin and a sulfonylurea. This triple therapy regimen is not an approved indication.

Treatment with thiazolidinediones has been associated with cases of congestive heart failure, some of which were difficult to treat unless the medication was discontinued. TEVA-ROSIGLITAZONE should be discontinued if any deterioration in cardiac status occurs.

TEVA-ROSIGLITAZONE is contraindicated in patients with NYHA Class I, II, III and IV heart failure. Patients with severe heart failure (including NYHA Class III and IV cardiac status) were not studied during the clinical trials.

Edema and heart failure have been reported more frequently in elderly patients. Caution should be exercised in patients over 75 years because of the limited experience in this patient group.

**Ischemic heart disease:** In a retrospective analysis of data from pooled clinical studies, (n=14,237), which included patients on combination therapy with insulin as well as patients with NYHA Class I and II heart failure, the overall incidence of events typically associated with cardiac ischemia was higher for rosiglitazone maleate containing regimens, 2.00% versus comparators, 1.53% [Hazard ratio 1.30 (95% confidence interval 1.004 - 1.69)].

In a subgroup analysis of these data, this risk was further increased in patients receiving nitrates with approximately twice as many events in patients receiving rosiglitazone versus comparators. **The use of TEVA-ROSIGLITAZONE is therefore not recommended for patient being treated with nitrates.**

In a meta-analyses of 52 double-blind, randomized, controlled clinical trials (mean duration 6 months) (n=16,995) statistically significant increases in myocardial infarction (Odds ratio (OR)= 1.80; 95% CI= [1.03, 3.25]), serious myocardial ischemic events (OR= 1.46; 95% CI= [1.06, 2.03]) and total myocardial ischemic events (OR= 1.34; 95% CI= [1.07, 1.70]) were demonstrated. A nearly statistically significant increase was shown for major adverse cardiovascular events (MACE) (OR= 1.44; 95% CI= [0.95, 2.20]). Non-statistically significant increases were also shown for CV death (OR= 1.46; 95% CI= [0.60, 3.77]) and all-cause death (OR=1.38; 95% CI= [0.72, 2.72]). The odds ratios for congestive heart failure and stroke were OR=1.93; 95% CI= [1.30, 2.93] and OR= 0.86; 95% CI= [0.40, 1.83], respectively.

***Patients with a history of Ischemic Heart Disease:*** There are limited clinical trial data in patients with ischemic heart disease. In a subgroup of rosiglitazone users with a history of Ischemic Heart Disease of a large cardiovascular outcomes trial (383 out of 2220 patients) there was a non-significant increase in the primary endpoint of cardiovascular death or cardiovascular hospitalization (Hazard Ratio 1.26; 95% CI [0.95, 1.68]). **TEVA-ROSIGLITAZONE is not recommended in patients with a history of ischemic heart disease, particularly those with myocardial ischemic symptoms.**

**Edema:** TEVA-ROSIGLITAZONE should be used with caution in patients with edema. In healthy volunteers who received rosiglitazone maleate 8 mg once daily as monotherapy for 8 weeks, there was a statistically significant increase in median plasma volume (1.8 mL/kg) compared to placebo. In controlled clinical trials of patients with Type 2 diabetes, mild to

moderate edema was observed at a greater frequency in patients treated with rosiglitazone maleate and may be dose related (see ADVERSE REACTIONS). For information on macular edema, see WARNINGS and PRECAUTIONS, Ophthalmologic.

Edema and heart failure have been reported more frequently in elderly patients. Caution should be exercised in patients over 75 years because of the limited experience in this patient group.

**Endocrine and Metabolism**

**Loss of control of blood glucose:** 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 TEVA-ROSIGLITAZONE and temporarily administer insulin. TEVA-ROSIGLITAZONE may be reinstituted after the acute episode is resolved.

**Hypoglycemia:** Because rosiglitazone maleate does not stimulate insulin secretion, hypoglycemia is not expected to occur when TEVA-ROSIGLITAZONE is prescribed as monotherapy. Patients receiving TEVA-ROSIGLITAZONE in combination with other hypoglycemic agents (e.g. insulin secreting agents) may be at risk for hypoglycemia, and a reduction in the dose of either agent may be necessary.

**Weight Gain:** Dose-related weight gain was seen with rosiglitazone maleate alone and in combination with other hypoglycemic agents. Treatment should be re-evaluated in patients with excessive weight gain (see ACTION AND CLINICAL PHARMACOLOGY and ADVERSE REACTIONS).

**Fractures:** Long-term studies showed an increased incidence of bone fractures in patients taking rosiglitazone maleate. In females, this increased incidence was noted after the first year of treatment and persisted during long-term treatment. The majority of the fractures have occurred in the upper limbs and distal lower limbs (see ADVERSE REACTIONS). The risk of fracture should be considered in the care of all patients treated with rosiglitazone maleate.

**Hematologic**

In controlled trials, there were dose decreases in hemoglobin and hematocrit. The magnitude of the decreases (≤ 11 g/L for hemoglobin and ≤ 0.034 for hematocrit) was small for rosiglitazone maleate alone and rosiglitazone maleate in combination with metformin or in combination with sulfonylurea. The changes occurred primarily during the first 3 months of therapy or following an increase in rosiglitazone maleate dose and remained relatively constant thereafter. Decreases may be related to increased plasma volume observed during treatment with rosiglitazone maleate and have not been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry). Patients with a hemoglobin value of < 110 g/L for males and < 100 g/L for females were excluded from the clinical trials.

**Hepatic**

**Therapy with TEVA-ROSIGLITAZONE should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 times the upper limit of normal).**

Rare cases of severe hepatocellular injury have been reported with thiazolidinediones.

In postmarketing experience with rosiglitazone maleate, reports of hepatitis and of hepatic enzyme elevations to three or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Liver enzymes should be checked prior to the initiation of therapy with TEVA-ROSIGLITAZONE in all patients and periodically thereafter per the clinical judgement of the healthcare professional.

Patients with mildly elevated liver enzymes (ALT levels $\leq$ 2.5 times the upper limit of normal) at baseline or during therapy with TEVA-ROSIGLITAZONE should be evaluated to determine the cause of the liver enzymes elevation.

Initiation of, or continuation of, therapy with rosiglitazone maleate in patients with mild liver enzyme elevations (ALT levels $\leq$ 2.5 times the upper limit of normal) should proceed with caution and include appropriate 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 > 3 times the upper limit of normal in patients on therapy with rosiglitazone maleate, liver enzymes levels should be rechecked as soon as possible. If ALT levels remain > 3 times the upper limit of normal, therapy with TEVA-ROSIGLITAZONE should be discontinued (see DOSAGE AND ADMINISTRATION).

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

**Ophthalmologic**

New onset and/or worsening macular edema with decreased visual acuity has been reported rarely in postmarketing experience with rosiglitazone maleate. In some cases, the visual events resolved or improved following discontinuation of rosiglitazone maleate. Physicians should consider the possibility of macular edema if a patient reports disturbances in visual acuity (see Post-Market Adverse Drug Reactions).

**Sexual Function/Reproduction**

**Ovulation:** As with other thiazolidinediones, rosiglitazone maleate may result in resumption of ovulation in premenopausal, anovulatory women with insulin resistance (e.g., patients with polycystic ovary syndrome). **As a consequence of their improved insulin sensitivity, these patients may be at risk of pregnancy if adequate contraception is not used.**

Although hormonal imbalance has been seen in preclinical studies (see TOXICOLOGY, Carcinogenesis, Mutagenesis, Impairment of Fertility), no significant adverse experiences associated with menstrual disorders have been reported in clinical trial participants, including premenopausal women. If unexpected menstrual dysfunction occurs, the benefits of continued therapy should be reviewed.

**Renal**

No dose adjustment is required in patients with mild and moderate renal insufficiency.

Limited data are available in patients with severe renal insufficiency (creatinine clearance < 30 ml/min) and therefore rosiglitazone should be used with caution in these patients (see DOSAGE AND ADMINISTRATION, Dosing Considerations, and ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency).

**Special Populations**

**Pregnant Women:** There are no controlled trials of rosiglitazone maleate in pregnant women. Rosiglitazone has been reported to cross the human placenta and to be detectable in fetal tissues. TEVA-ROSIGLITAZONE is contraindicated for use in pregnant women. Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. In animal studies, rosiglitazone maleate was not teratogenic but treatment during mid-late gestation caused fetal death and growth retardation in both rats and rabbits at 19- and 73-fold clinical systemic exposure, respectively (see TOXICOLOGY, Teratogenic Effects).

**Labour and Delivery:** The effect of rosiglitazone on labour and delivery in humans is not known.

**Nursing Women:** It is not known whether rosiglitazone maleate is excreted in human milk. Because many drugs are excreted in human milk, TEVA-ROSIGLITAZONE should not be administered to a nursing woman.

**Pediatrics (< 18 years of age)**: There are no data on the use of rosiglitazone maleate in patients under 18 years of age; therefore, TEVA-ROSIGLITAZONE is not indicated for use in patients under 18 years of age. Thiazolidinediones promote the maturation of preadipocytes and have been associated with weight gain. Obesity is a major problem in adolescents with type 2 diabetes.

**Geriatrics (≥ 65 years of age):** Evidence from clinical studies and experience suggest that use in the geriatric population may be associated with differences in safety See WARNINGS & PRECAUTIONS, Cardiovascular.

**Monitoring and Laboratory Tests**

Periodic fasting blood glucose and A1C measurements should be performed to monitor therapeutic response.

Liver enzyme monitoring is recommended prior to initiation of therapy with TEVA-ROSIGLITAZONE in all patients and periodically thereafter (see WARNINGS AND PRECAUTIONS, Hepatic).

## ADVERSE REACTIONS

**Adverse Drug Reaction Overview**

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

In clinical trials, edema was reported in 4.8% of patients taking rosiglitazone maleate as monotherapy compared to 1.3% on placebo, 1.0% on sulfonylureas and 2.2% on metformin. Treatment was required for 1.2% of patients on rosiglitazone monotherapy with an adverse event of edema. These adverse experiences rarely led to withdrawal. In these clinical trials, few patients (1.0%) were enrolled with a presenting medical condition of congestive heart failure (NYHA Class I/II). Edema was more frequently observed when rosiglitazone maleate was used in combination with a sulfonylurea or insulin (see WARNINGS AND PRECAUTIONS, General, and Cardiovascular; and CLINICAL TRIALS).

In clinical trials, an increased incidence of heart failure has also been observed when rosiglitazone maleate was added to a sulfonylurea (see WARNINGS AND PRECAUTIONS, Cardiovascular).

In double blind studies where rosiglitazone maleate was administered for up to one year, serious adverse experiences of ischemic heart disease were reported in 1.3% of patients taking rosiglitazone maleate compared to 0.5% on placebo, 0.8% on sulfonylureas and 1.3% on metformin.

In a retrospective analysis of data from pooled clinical studies, which included patients on combination therapy with insulin as well as patients with NYHA Class I and II heart failure, the overall incidence of events typically associated with cardiac ischemia was higher for rosiglitazone maleate containing regimens, 2.00% versus comparators, 1.53% [Hazard ratio 1.30 (95% confidence interval 1.004 - 1.69)].

In a subgroup analysis of this data, this risk was further increased in patients receiving nitrates with approximately twice as many events in patients receiving rosiglitazone versus comparators (see WARNINGS AND PRECAUTIONS, Cardiovascular, Ischemic heart disease).

In a meta-analyses of 52 double-blind, randomized, controlled clinical trials (mean duration 6 months) (n=16,995) statistically significant increases in myocardial infarction (Odds ratio (OR)= 1.80; 95% CI= [1.03, 3.25]), serious myocardial ischemic events (OR= 1.46; 95% CI= [1.06, 2.03]) and total myocardial ischemic events (OR= 1.34; 95% CI= [1.07, 1.70]) were demonstrated. A nearly statistically significant increase was shown for major adverse cardiovascular events (MACE) (OR= 1.44; 95% CI= [0.95, 2.20]). Non-statistically significant increases were also shown for CV death (OR= 1.46; 95% CI= [0.60, 3.77]) and all-cause death (OR=1.38; 95% CI= [0.72, 2.72]). The odds ratios for congestive heart failure and stroke were OR=1.93; 95% CI= [1.30, 2.93] and OR= 0.86; 95% CI= [0.40, 1.83], respectively.

In a subgroup of rosiglitazone users with a history of Ischemic Heart Disease of a large cardiovascular outcomes trial (383 out of 2220 patients) there was a non-significant increase in the primary endpoint of cardiovascular death or cardiovascular hospitalization (Hazard Ratio 1.26; 95% CI [0.95, 1.68]) (see WARNINGS AND PRECAUTIONS, Cardiovascular, Ischemic heart disease, Patients with a history of Ischemic Heart Disease).

In clinical trials, dose-related weight gain was seen with rosiglitazone maleate alone and in combination with other hypoglycemic agents (see ACTION AND CLINICAL PHARMACOLOGY and WARNINGS AND PRECAUTIONS). In a long-term monotherapy trial (ADOPT) in drug-naïve patients, median weight change (range) at 4 years was 3.5 kg (-31.0 to 41.3) for rosiglitazone maleate, 2.0 kg (-28.6 to 24.9) for glyburide, and 2.4 kg (-46.0 to 12.9)

for metformin. This weight change with rosiglitazone maleate occurred consistently over the duration of the study (see CLINICAL TRIALS).

Long-term studies showed an increased incidence of bone fracture in patients taking rosiglitazone maleate (see WARNINGS AND PRECAUTIONS, Fractures, and ADVERSE REACTIONS, Clinical Trial Drug Adverse Reactions)

Increased appetite was observed in clinical trials of rosiglitazone as monotherapy or concomitantly with a sulfonylurea.

Hypoglycemia was generally mild to moderate in nature and was dose-related when rosiglitazone was used in combination with metformin or a sulfonylurea. Patients receiving rosiglitazone in combination with oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of either agent may be necessary.

In double blind studies, anemia was reported in 1.9% of patients taking rosiglitazone maleate as monotherapy compared to 0.7% on placebo, 0.6% on sulfonylureas and 2.2% on metformin. Treatment was required for 0.3% of patients with an adverse event of anemia. These adverse experiences rarely led to withdrawal. Reports of anemia were greater in patients treated with a combination of rosiglitazone maleate and metformin (7.1%) compared to monotherapy with rosiglitazone maleate or rosiglitazone maleate in combination with a sulfonylurea (2.3%). Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anemia in these studies.

Constipation was observed to be generally mild to moderate in nature during clinical trials of rosiglitazone as monotherapy, or concomitantly with metformin or a sulfonylurea.

## Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

### Controlled Clinical Trials:

The overall incidence and types of adverse experiences reported in clinical trials of rosiglitazone (16 weeks to 1 year) as monotherapy or in combination with metformin or sulfonylurea are shown in Table 1.

**Table 1: Adverse Experiences (≥ 5% in Any Treatment Group) Reported by Patients in Double-blind Clinical Trials with Rosiglitazone Maleate as Monotherapy**

| | Rosiglitazone Maleate N = 2526 | | Placebo N = 601 | | Metformin N = 225 | | Sulfonylureas N = 626 | |
|---|---|---|---|---|---|---|---|---|
| **Preferred Term** | n | **%** | n | **%** | n | **%** | n | **%** |
| **Total Pts w/adverse experiences** | 1742 | **69.0** | 374 | **62.2** | 172 | **76.0** | 438 | **70.0** |
| Upper respiratory tract | 251 | **9.9** | 52 | **8.7** | 20 | **8.9** | 46 | **7.3** |

| | Rosiglitazone Maleate N = 2526 | | Placebo N = 601 | | Metformin N = 225 | | Sulfonylureas N = 626 | |
|---|---|---|---|---|---|---|---|---|
| infection | | | | | | | | |
| Injury* | 192 | **7.6** | 26 | **4.3** | 17 | **7.6** | 38 | **6.1** |
| Headache | 148 | **5.9** | 30 | **5.0** | 20 | **8.9** | 34 | **5.4** |
| Back pain | 102 | **4.0** | 23 | **3.8** | 9 | **4.0** | 31 | **5.0** |
| Hyperglycemia | 99 | **3.9** | 34 | **5.7** | 10 | **4.4** | 51 | **8.1** |
| Fatigue | 92 | **3.6** | 30 | **5.0** | 9 | **4.0** | 12 | **1.9** |
| Sinusitis | 82 | **3.2** | 27 | **4.5** | 12 | **5.3** | 19 | **3.0** |
| Diarrhea | 59 | **2.3** | 20 | **3.3** | 35 | **16** | 19 | **3.0** |
| Hypoglycemia | 16 | **0.6** | 1 | **0.2** | 3 | **1.3** | 37 | **5.9** |

* includes cuts, burns, sprains, fractures, falls, accidents and surgical procedures.

Overall, the types of adverse experiences reported when rosiglitazone maleate was used in combination with a sulfonylurea or metformin were similar to those during monotherapy with rosiglitazone maleate.

**Long-term Trials of rosiglitazone maleate:** In a 4 to 6 year monotherapy study (ADOPT), adverse reactions observed with rosiglitazone maleate were generally consistent to those observed in shorter-term trials as presented in Table 1, above (see CLINICAL TRIALS). However, fractures were reported in a greater number of females with rosiglitazone (9.3%, 2.7/100 patient-years) compared to glyburide (3.5%, 1.3/100 patient-years) or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the females who received rosiglitazone maleate were reported in the upper arm, hand and foot (see WARNINGS AND PRECAUTIONS, Fractures).

In a multi-centre, randomized, open-label study with a mean follow-up of 5.5 years, there was an increased incidence of bone fractures for subjects randomized to rosiglitazone maleate in addition to metformin or sulfonylurea compared to those randomized to metformin plus sulfonylurea (see WARNINGS AND PRECAUTIONS, Fractures). The risk of fracture was higher in females relative to control than in males relative to control.

**Table 2 Summary of Bone Fractures by Overall Rate, Gender and Relative Risk During CV Follow-up (ITT Population)**

| **Bone fracture (female and male); n (%) subjects [no. of events]** | **RSG (N=2220)** | **MET/SU (N=2227)** | **Relative risk (95% CI)** | **p-value** |
|---|---|---|---|---|
| **Any event** | 185 (8.3) [225] | 118 (5.3) [132] | 1.57 (1.26, 1.97) | p <0.001 |
| Upper limb | 86 (3.9) [101] | 55 (2.5) [58] | 1.57 (1.12, 2.19) | p=0.0095 |
| Distal lower limb | 70 (3.2) [101] | 27 (1.2) [28] | 2.60 (1.67, 4.04) | p<0.001 |
| Femur/hip | 10 (0.5) [11] | 8 (0.4) [8] | 1.25 (0.50, 3.17) | |
| Spine | 14 (0.6) [14] | 9 (0.4) [9] | 1.56 (0.68, 3.60) | |
| Pelvis | 0 | 4 (0.2) [4] | NA | |
| Other | 25 (1.1) [26] | 25 (1.1) [25] | 1.00 (0.58, 1.74) | |
| **Bone fracture in female subjects, n (%) subjects [no. of events]** | **RSG (N=1078)** | **MET/SU (N=1075)** | **Relative risk (95% CI)** | **p-value** |
| **Any event** | 124 (11.5)[154] | 68 (6.3) [78] | 1.82 (1.37, 2.41) | p<0.001 |
| Upper limb | 63 (5.8) [78] | 36 (3.3) [39] | 1.75 (1.17, 2.61) | p=0.0075 |
| Distal lower limb | 47 (4.4) [49] | 16 (1.5) [17] | 2.93 (1.67, 5.13) | p<0.001 |

| | | | | |
|---|---|---|---|---|
| Femur/hip | 7 (0.6) [8] | 7 (0.7) [7] | 1.00 (0.35, 2.83) | |
| Spine | 8 (0.7) [8] | 4 (0.4) [4] | 1.99 (0.60, 6.60) | |
| Pelvis | 0 | 1 (<0.1) [1] | NA | |
| Other | 11 (1.0) [11] | 10 (0.9) [10] | 1.10 (0.46, 1.94) | |
| **Bone fracture in male subjects, n (%) subjects [no. of events]** | **RSG (N=1142)** | **MET/SU (N=1152)** | **Relative risk (95% CI)** | **p-value** |
| **Any event** | 61 (5.3) [71] | 50 (4.3) [54] | 1.23 (0.85, 1.77) | p=0.3160 |
| Upper limb | 23 (2.0) [23] | 19 (1.6) [19] | 1.22 (0.67, 2.23) | p=0.6261 |
| Distal lower limb | 23 (2.0) [24] | 11 (1.0) [11] | 2.11 (1.03, 4.31) | p=0.0521 |
| Femur/hip | 3 (0.3) [3] | 1 (<0.1) [1] | 3.03 (0.32, 29.05) | |
| Spine | 6 (0.5) [6] | 5 (0.4) [5] | 1.21 (0.37, 3.96) | |
| Pelvis | 0 | 3 (0.3) [3] | NA | |
| Other | 14 (1.2) [15] | 15 (1.3) [15] | 0.94 (0.46, 1.94) | |

## Abnormal Hematologic and Clinical Chemistry Findings

**Hematological:** Small decreases in hematological parameters were more common in the patients treated with rosiglitazone maleate than in placebo-treated patients. Leukopenia was reported in 0.4% of rosiglitazone maleate patients compared to 0.2% of patients on placebo, 0.6% on sulfonylureas and 0% on metformin. Decreases may be related to increased plasma volume observed with treatment with rosiglitazone maleate. The mean decrease in hemoglobin was approximately 10 to 12 g/L; the decrease in hematocrit was 0.03 to 0.04.

**Lipids:** Small increases in total cholesterol and LDL have been observed following treatment with rosiglitazone maleate (see Table 3, ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

**Serum Transaminase Levels:** In clinical studies in 4598 patients treated with rosiglitazone maleate encompassing approximately 3600 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevated ALT levels.

In the controlled trials (including patients with ALT/AST of up to 2.5 times the upper limit of the reference range at study entry), 0.2% of patients treated with rosiglitazone maleate had reversible elevations in ALT > 3 times the upper limit of the reference range compared to 0.2% on placebo, 0.9% on metformin and 0.3% on sulfonylureas.

Hyperbilirubinemia was found in 0.3% of patients treated with rosiglitazone maleate compared with 0.9% treated with placebo. Overall, there was a decrease in mean values for ALT, AST, alkaline phosphatase and bilirubin over time in patients treated with rosiglitazone maleate (see WARNINGS AND PRECAUTIONS, Hepatic).

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

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure.

## Post-Market Adverse Drug Reactions

In postmarketing experience with rosiglitazone maleate as monotherapy and in combination with other antidiabetic agents, adverse events potentially related to volume expansion (e.g., congestive heart failure, pulmonary edema, and pleural effusions) have been reported (see WARNINGS AND PRECAUTIONS, Cardiovascular).

Reports of events related to cardiovascular ischemia including myocardial infarction, and hypertension or hypertension accelerated have been received.

Reports of new onset and/or worsening macular edema with decreased visual acuity occurring with the use of rosiglitazone maleate have been received rarely. These patients frequently reported concurrent peripheral edema. In some cases, symptoms improved following discontinuation of rosiglitazone maleate (see WARNINGS AND PRECAUTIONS, Ophthalmologic).

Reports of anaphylactic reaction (such as angioedema and urticaria), rash and pruritus have been received very rarely.

Long-term post-market studies have shown an increased incidence of bone fracture in patients taking rosiglitazone maleate (see WARNINGS AND PRECAUTIONS, Fractures; and ADVERSE REACTIONS, Clinical Trial Drug Adverse Reactions).

Reports of hepatitis and of hepatic enzyme elevations to three or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established.

Postmarketing reports of parotid gland enlargement have been associated with rosiglitazone and approximately one third of the reports resolved or improved following discontinuation of rosiglitazone maleate.

# DRUG INTERACTIONS

## Overview

**Drugs Metabolized by Cytochrome $P_{450}$:** It has been shown *in vitro* that rosiglitazone maleate does not inhibit any of the major $P_{450}$ enzymes at clinically relevant concentrations. *In vitro* studies demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, with CYP2C9 as only a minor pathway. *In vitro* studies have shown that montelukast is an inhibitor of CYP2C8 and may inhibit the metabolism of drugs primarily metabolized by CYP2C8 (e.g. paclitaxel, rosiglitazone, repaglinide). No *in vivo* interaction studies have been performed with the CYP2C8 inhibitor, montelukast; or, with CYP2C8 substrates cerivastatin and paclitaxel. The potential for a clinically relevant interaction with cerivastatin is considered to be low. Although rosiglitazone is not anticipated to affect the pharmacokinetics of paclitaxel, concomitant use is likely to result in inhibition of the metabolism of rosiglitazone.

Co-administration of rosiglitazone with CYP2C8 inhibitors (e.g. gemfibrozil) resulted in increased rosiglitazone plasma concentrations. Since there is a potential for an increase in the risk of dose-related adverse reactions, a decrease in rosiglitazone may be needed when CYP2C8 inhibitors are co-administered.

Co-administration of rosiglitazone with a CYP2C8 inducer (e.g. rifampin) resulted in decreased rosiglitazone plasma concentrations. Therefore, close monitoring of glycemic control and changes in diabetic treatment should be considered when CYP2C8 inducers are co-administered.

Clinically significant interactions with CYP2C9 substrates or inhibitors are not anticipated.

**CYP3A4 Substrates:** Rosiglitazone maleate (8 mg once daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinylestradiol and norethindrone), which are predominantly metabolized by CYP3A4. The results of these two drug interaction studies suggest that rosiglitazone maleate is unlikely to cause clinically important drug interactions with other drugs metabolized via CYP3A4.

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

**Drug-Drug Interactions**

**Oral Contraceptives:** In 32 healthy women, rosiglitazone maleate (8 mg once daily) was shown to have no statistically significant effect on the pharmacokinetics of oral contraceptives (ethinylestradiol and norethindrone). Breakthrough bleeding occurred in 5 individuals when rosiglitazone maleate was co-administered with an oral contraceptive. In one of these subjects a 40% decrease in ethinylestradiol exposure (AUC) was recorded. This was not correlated with a reduction in exposure to norethindrone, nor was there a consistent relationship between the occurrence of breakthrough bleeding and the pharmacokinetics of either ethinylestradiol or norethindrone in individual subjects.

**Glyburide:** Rosiglitazone maleate (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.

**Glimepiride:** Single oral doses of glimepiride in 14 healthy adult subjects had no clinically significant effect on the steady-state pharmacokinetics of rosiglitazone maleate. No clinically significant reductions in glimepiride AUC and Cmax were observed after repeat doses of rosiglitazone maleate for 8 days in healthy adult subjects.

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

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

**Digoxin:** Repeat oral dosing of rosiglitazone maleate (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:** Coadministration of rosiglitazone maleate (4 mg twice daily for 7 days) did not alter the anticoagulant response of steady-state warfarin in healthy volunteers with baseline values of INR of < 2.75. Repeat dosing with rosiglitazone maleate had no clinically relevant effect on the steady-state pharmacokinetics of warfarin.

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

**Fibrates:** Some epidemiologic studies and case reports suggest that markedly decreased HDL-C in some patients involve the interaction of rosiglitazone with fenofibrate or bezafibrate. Laboratory findings in some case reports demonstrated that, in some cases, it is the combination of rosiglitazone and fenofibrate, and neither agent alone that lowers HDL-C.

A study conducted in normal healthy volunteers showed that gemfibrozil (an inhibitor of CYP2C8) administered as 600 mg twice daily, increased rosiglitazone systemic exposure two-fold at steady state (see WARNINGS AND PRECAUTIONS, General).

**Rifampin:** A study conducted in normal healthy volunteers showed that rifampin (an inducer of CYP2C8) administered as 600 mg daily, decreased the rosiglitazone systemic exposure three-fold (see WARNINGS AND PRECAUTIONS, General).

**Methotrexate:** An interaction study of 22 adult patients with psoriasis examined the effect of repeat doses of rosiglitazone (8 mg daily as a single dose for 8 days) on the pharmacokinetics of oral methotrexate administered as single oral doses of 5 to 25 mg weekly. Following 8 days of rosiglitazone administration, the $C_{max}$ and $AUC_{(0\text{-}inf)}$ of methotrexate increased by 18% (90% CI: 11% to 26%) and 15% (90% CI: 8% to 23%), respectively, when compared to the same doses of methotrexate administered in the absence of rosiglitazone.

**Concomitant Medications in Phase III Clinical Trials:** Results of the population pharmacokinetic analysis indicated that none of the following classes of concomitant medications (oral hypoglycemics, analgesics, calcium channel blockers, hypolipidemics, ACE inhibitors and steroid hormones) appear to alter the oral clearance or oral steady-state volume of distribution of rosiglitazone maleate.

**Drug-Food Interactions**
Interactions with food have not been established.

**Drug-Herb Interactions**
Interactions with herbal products have not been established.

**Drug-Laboratory Test Interactions**
Interactions with laboratory tests have not been established.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

The management of antidiabetic therapy should be individualized.

Increases in rosiglitazone to 8 mg/day should be undertaken cautiously following appropriate clinical evaluation to assess the patient's risk of developing adverse reactions relating to fluid retention (see WARNINGS AND PRECAUTIONS; ADVERSE REACTIONS; and CLINICAL TRIALS). The dose of TEVA-ROSIGLITAZONE used in combination with a sulfonylurea

should not exceed 4 mg daily (see Recommended Dose and Dosage Adjustment, Combination Therapy with sulfonylurea).

TEVA-ROSIGLITAZONE may be administered as a single daily dose in the morning, or divided and administered in the morning and evening.

TEVA-ROSIGLITAZONE may be taken with or without food.

No dosage adjustments are required for the elderly, or in patients with mild and moderate renal impairment. Limited data are available in patients with severe renal insufficiency (creatinine clearance < 30 ml/min) and therefore rosiglitazone should be used with caution in these patients (see WARNINGS AND PRECAUTIONS, Renal, and ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency).Therapy with TEVA-ROSIGLITAZONE should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT > 2.5 times the upper limit of normal at start of therapy). TEVA-ROSIGLITAZONE is contraindicated in patients with serious hepatic impairment. See CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Hepatic and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency.

**Recommended Dose and Dosage Adjustment**

**Monotherapy**
The usual starting dose of TEVA-ROSIGLITAZONE is 4 mg administered either as a single dose once daily or in divided doses twice daily. For patients who respond inadequately following 8 to 12 weeks of treatment as determined by reduction in fasting plasma glucose (FPG), the dose may be increased to 8 mg administered as a single dose once daily or in divided doses twice daily.

**Combination Therapy with Metformin**
The usual starting dose of TEVA-ROSIGLITAZONE in combination with metformin is 4 mg administered as either a single dose once daily or in divided doses twice daily. The dose of TEVA-ROSIGLITAZONE may be increased to 8 mg/day following 8 to 12 weeks of therapy if there is insufficient reduction in FPG.

**Combination Therapy with Sulfonylurea**
The recommended dose of TEVA-ROSIGLITAZONE when used in combination with sulfonylurea is 4 mg administered as either a single dose once daily or in divided doses twice daily. The dose of TEVA-ROSIGLITAZONE used in combination with a sulfonylurea should not exceed 4 mg daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased (see WARNINGS AND PRECAUTIONS; and ADVERSE REACTIONS).

**Missed Dose**

If a dose of TEVA-ROSIGLITAZONE is missed with once a day dosing, the patient should be advised to take the dose as soon as they remember anytime during the day. If a dose is missed with twice a day dosing, the patient should be advised to take the missed dose as soon as they remember and the next dose at the usual time. Three doses should never be taken in one day to make up for a missed dose the day before. If a whole day of TEVA-ROSIGLITAZONE is missed, the usual dosing schedule should be followed the next day without making up for the missed doses.

## OVERDOSAGE

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

Limited data are available with regard to overdosage in humans. In clinical studies in volunteers, rosiglitazone maleate has been administered at single oral doses of up to 20 mg and was well tolerated.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

TEVA-ROSIGLITAZONE is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity in type 2 diabetes. Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves glycemic control while reducing circulating insulin levels. It improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Rosiglitazone is not chemically or functionally related to the sulfonylureas, the biguanides or the alpha-glucosidase inhibitors. 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 and in the maturation of preadipocytes, predominantly of subcutaneous origin.

Insulin resistance is a primary feature characterizing the pathogenesis of type 2 diabetes. TEVA-ROSIGLITAZONE results in increased responsiveness of insulin-dependent tissues and significantly improves hepatic and peripheral (muscle) tissue sensitivity to insulin in patients with type 2 diabetes. Clinical studies in patients with type 2 diabetes treated with rosiglitazone maleate either as monotherapy or in combination with metformin or sulfonylureas showed improved beta-cell function and decreased fasting plasma glucose, insulin and C-peptide values following 26 weeks of treatment. In a 4 to 6 year monotherapy study in drug-naïve patients, rosiglitazone treated patients showed an improvement in insulin sensitivity. The initial improvement in beta-cell function observed with rosiglitazone maleate was not sustained and gradually declined after one year for the duration of the study but continued to remain above baseline, as was the case for metformin and glyburide. A homeostasis model assessment (HOMA) was conducted using fasting plasma glucose and insulin or C-peptide levels as a measure of insulin sensitivity and beta-cell function. In these studies, reductions in mean plasma pro-insulin and pro-insulin split product concentrations were also observed.

Rosiglitazone maleate significantly reduced hemoglobin A1C (A1C, a marker for long term glycemic control), and fasting blood glucose (FBG) in patients with type 2 diabetes. Inadequately controlled hyperglycemia is associated with an increased risk of diabetic complications, including cardiovascular disorders and diabetic nephropathy, retinopathy and neuropathy.

Studies between 8 and 26 weeks with rosiglitazone maleate have shown a statistically significant reduction in markers of inflammation, C-reactive protein (CRP) and matrix metalloproteinase-9

(MMP-9). The clinical significance of these effects are still unknown. Further long term clinical trials are needed.

Estimates of LDL particle size can be determined by the LDL cholesterol (LDL) to apolipoprotein B (Apo B) ratio. In controlled clinical trials, rosiglitazone has been shown to increase the LDL cholesterol to Apo B ratio consistent with a beneficial change in LDL particle size from small dense LDL particles to larger more buoyant particles. This change has been confirmed by measuring LDL particle buoyancy (Rf) following 8 weeks treatment with rosiglitazone in an open-label study.

**Pharmacodynamics and Clinical Effects**

In clinical studies, treatment with rosiglitazone maleate resulted in an improvement in glycemic control, as measured by fasting plasma glucose (FPG) and hemoglobin A1C (HbA1C), with a concurrent reduction in insulin and C-peptide. Post-prandial glucose and insulin levels were also reduced. This is consistent with the mechanism of action of TEVA-ROSIGLITAZONE as an insulin sensitizer. The improvement in glycemic control was durable, with maintenance of effect for at least 52 weeks. In open-labelled extension studies sustained improvements in glycemic control (as measured by A1C levels) were observed in patients receiving rosiglitazone monotherapy for 36 months. The maximum recommended daily dose of TEVA-ROSIGLITAZONE is 8 mg. Phase II studies indicated that no additional benefit was obtained with a total daily dose of 12 mg.

Rosiglitazone maleate is believed to act primarily on muscle and adipose tissue whereas metformin acts primarily on the liver to decrease hepatic glucose output. The co-administration of rosiglitazone maleate with either metformin or sulfonylurea resulted in significantly improved glycemic control compared to any of these agents alone. These results are consistent with a synergistic effect on glycemic control when rosiglitazone maleate is used in combination therapy. In patients whose type 2 diabetes was inadequately controlled with metformin or sulfonylurea monotherapy, the addition of rosiglitazone led to reductions in A1C levels that were sustained for over 30 months of treatment, in open-labelled studies.

Weight gain has been observed in clinical studies with rosiglitazone maleate (see Table 3). In addition, rosiglitazone maleate significantly decreased visceral (abdominal) fat stores while increasing subcutaneous abdominal fat. The reduction in visceral fat correlates with improved hepatic and peripheral tissue insulin sensitivity. Weight gain with thiazolidinediones can result from increases in subcutaneous adipose tissue and/or from fluid retention. Treatment should be re-evaluated in patients with excessive weight gain (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

**Table 3: Weight Changes (kg) from Baseline During Clinical Trials with Rosiglitazone maleate**

| Treatment Group | Duration | Control Group | Control Group | Rosiglitazone maleate 4 mg | Rosiglitazone maleate 8 mg |
|---|---|---|---|---|---|
| | | | median ($25^{th}$, $75^{th}$ percentile) (range) | median ($25^{th}$, $75^{th}$ percentile) (range) | median ($25^{th}$, $75^{th}$ percentile) (range) |
| **Monotherapy** | | | | | |
| Rosiglitazone maleate | 26 weeks | placebo | -0.9<br>(-2.8, 0.9)<br>(-9.6 to 6.8)<br>n = 210 | 1.0<br>(-0.9, 3.6)<br>(-11.6 to 12.7)<br>n = 436 | 3.1<br>(1.1, 5.8)<br>(-6.8 to 13.9)<br>n = 439 |

| Treatment Group | Duration | Control Group | Control Group | Rosiglitazone maleate 4 mg | Rosiglitazone maleate 8 mg |
|---|---|---|---|---|---|
| | | | median ($25^{th}$, $75^{th}$ percentile) (range) | median ($25^{th}$, $75^{th}$ percentile) (range) | median ($25^{th}$, $75^{th}$ percentile) (range) |
| Rosiglitazone maleate | 52 weeks | sulfonylurea | 2.0<br>(0, 4.0)<br>(-11.5 to 12.2)<br>n = 173 | 2.0<br>(-0.6, 4.0)<br>(-7.0 to 16.0)<br>n = 150 | 2.6<br>(0, 5.3)<br>(-11.0 to 22.0)<br>n = 157 |
| Rosiglitazone maleate | 48 months | metformin | -2.4<br>(-5.4, 0.5)<br>(-46.0 to 12.9)<br>n = 1,441 | | 3.5<br>(0.0, 8.1)<br>(-31.0 to 41.3)<br>n = 1,456 |
| | | glyburide | 2.0<br>(-1.0, 4.8)<br>(-28.6 to 24.9)<br>n = 1,441 | | |
| **Combination Therapy** | | | | | |
| Rosiglitazone maleate + sulfonylurea | 26 weeks | sulfonylurea | 0<br>(-1.3, 1.2)<br>(-6.0 to 14.0)<br>n = 1043 | 1.8<br>(0, 3.1)<br>(-5.0 to 11.5)<br>n = 392 | - |
| Rosiglitazone maleate + metformin | 26 weeks | metformin | -1.4<br>(-3.2, 0.2)<br>(-7.7 to 5.9)<br>n = 175 | 0.8<br>(-1.0, 2.6)<br>(-6.8 to 9.8)<br>n = 100 | 2.1<br>(0, 4.3)<br>(-5.4 to 13.1)<br>n = 184 |

Patients with lipid abnormalities were not excluded from clinical trials of rosiglitazone maleate. In all 26-week controlled trials, across the recommended dose range, rosiglitazone maleate as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids. These changes were statistically significantly different from placebo or glyburide controls (Table 4).

Increases in LDL occurred primarily during the first 1 to 2 months of therapy with rosiglitazone maleate and LDL levels remained stable, but elevated above baseline throughout the trials. In contrast, HDL continued to rise over time. As a result, the LDL/HDL ratio peaked after 2 months of therapy and then appeared to decrease over time. Because of the temporal nature of lipid changes, the 52-week glyburide-controlled study is most pertinent to assess long-term effects on lipids. At baseline, week 26, and week 52, median LDL/HDL ratios were 3.0, 2.9, and 2.8, respectively for Rosiglitazone maleate 4 mg twice daily and the median total cholesterol/HDL ratios were 4.76, 4.52 and 4.35, respectively. The corresponding values for glyburide were 3.2, 2.9, and 2.7 for the median LDL/HDL ratios and 4.90, 4.61 and 4.36 for the median total cholesterol/HDL ratios.

The pattern of LDL and HDL changes following therapy with rosiglitazone maleate in combination with sulfonylurea or metformin were generally similar to those seen with rosiglitazone maleate in monotherapy.

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

**Table 4: Summary of Lipid Changes in 26-Week Placebo-Controlled and 26-Week/52-Week Glyburide-Controlled Monotherapy Studies**

| | Placebo-controlled Studies Week 26 | | | Glyburide-controlled Study Week 26 and Week 52 | | | |
|---|---|---|---|---|---|---|---|
| | | Rosiglitazone Maleate | | Glyburide titration | | Rosiglitazone Maleate 8 mg | |
| | Placebo | 4 mg daily | 8 mg daily | wk 26 | wk 52 | wk 26 | wk 52 |
| **Free Fatty Acids (mmol/L)** | | | | | | | |
| N | 207 | 428 | 436 | 181 | 168 | 166 | 145 |
| Baseline (median) | 0.61 | 0.58 | 0.61 | 0.92 | 0.92 | 0.93 | 0.93 |
| % change from baseline (median) | -4.0 | -15.6 | -23.5 | -5.5 | -9.7 | -26.7 | -24.7 |
| **LDL-cholesterol (mmol/L)** | | | | | | | |
| N | 190 | 400 | 374 | 175 | 160 | 161 | 133 |
| Baseline (median) | 3.15 | 3.26 | 3.19 | 3.68 | 3.55 | 3.62 | 3.62 |
| % change from baseline (median) | +2.5 | +10.3 | +14.8 | -3.7 | -3.3 | +7.1 | +7.3 |
| **HDL-cholesterol (mmol/L)** | | | | | | | |
| N | 208 | 429 | 436 | 184 | 170 | 170 | 145 |
| Baseline (median) | 1.06 | 1.14 | 1.09 | 1.17 | 1.18 | 1.19 | 1.19 |
| % change from baseline (median) | +8.2 | +10.3 | +11.3 | +4.7 | +8.0 | +13.2 | +17.4 |

The long term significance of the lipid changes is not known.

Because rosiglitazone maleate does not stimulate insulin secretion, hypoglycemia is not expected to occur when rosiglitazone maleate is prescribed as monotherapy. Patients receiving rosiglitazone maleate in combination with other hypoglycemic agents (e.g. insulin secreting agents) may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

As insulin sensitizers can only work in the presence of insulin, TEVA-ROSIGLITAZONE should not be used in patients with type 1 diabetes.

## Pharmacokinetics

Maximum plasma concentration ($C_{max}$) and the area under the curve ($AUC_{0\text{-}inf}$) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range (Table 4). The elimination half-life is 3 to 4 hours and is independent of dose.

**Table 5: Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral Doses (n=32)**

| Parameter | ***1 mg Fasting | 2 mg Fasting | 8 mg Fasting | 8mg Fed |
|---|---|---|---|---|
| AUC0-inf [ng.h/mL] | 358 (112) | 733 (184) | 2971 (730) | 2890 (795) |
| Cmax [ng/mL] | 76 (13) | 156 (42) | 598 (117) | 432 (92) |
| $T_{max}$ [h]* | 0.5 (0.5-1.5) | 1.0 (0.5-2.0) | 1.0 (0.5-1.5) | 2.0 (1.0-5.0) |
| Half-life [h] | 3.16 (0.72) | 3.15 (0.39) | 3.37 (0.63) | 3.59 (0.70) |
| CL/F** [L/h] | 3.03 (0.87) | 2.89 (0.71) | 2.85 (0.69) | 2.97 (0.81) |

*$T_{max}$ presented as median (range)
** CL/F= Oral Clearance
*** TEVA-ROSIGLITAZONE 1 mg tablet is not currently available.

**Absorption:** Rosiglitazone is rapidly and completely absorbed after oral administration with negligible first-pass metabolism. The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed by 1 hour after dosing. Administration of rosiglitazone with food resulted in no change in overall exposure (AUC) but there was a decrease in the $C_{max}$ (about 28%) and a delay in $T_{max}$ of 1.75 hours. These changes are not likely to be clinically significant and rosiglitazone maleate may be administered with or without food.

**Distribution:** The mean (SD) volume of distribution (Vss) of rosiglitazone after intravenous administration to healthy subjects is approximately 14.1 (3.1) litres. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

**Metabolism:** Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than the parent drug 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 $P_{450}$ (CYP) isoenzyme 2C8, with CYP2C9 contributing as only a minor pathway.

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

**Special Populations and Conditions**

Population pharmacokinetic analyses from three Phase III trials including 642 men and 405 women with type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume of distribution (Vss/F) were shown to increase with

increases in body weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted CL/F and Vss/F values varied by < 1.7-fold and 2.3-fold, respectively. Additionally, rosiglitazone CL/F was shown to be lower (about 6%) in female patients compared to males of the same body weight. The population mean CL/F of rosiglitazone for a typical male weighing 84 kg was 2.48 L/h. The Vss/F in an 84 kg patient was 17.9L. The inter-patient variability in CL/F and Vss/F were 31% and 23%, respectively.

**Pediatrics:** The safety and effectiveness of rosiglitazone have not been established in patients younger than 18 years of age, therefore, TEVA-ROSIGLITAZONE is not indicated in patients younger than 18 years of age. Thiazolidinediones promote the maturation of preadipocytes and have been associated with weight gain. Obesity is a major problem in adolescents with type 2 diabetes.

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

**Gender:** Results of the population pharmacokinetic analysis showed that the mean oral clearance of rosiglitazone in female patients (n=405) was 15% lower compared to male patients (n=642), primarily related to lower body weight in females.

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

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

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

**Hepatic Insufficiency:** Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound $C_{max}$ and $AUC_{0\text{-}inf}$ were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects. Therapy with TEVA-ROSIGLITAZONE should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT > 2.5 times the upper limit of normal) at baseline (see WARNINGS AND PRECAUTIONS, Hepatic).

**Renal Insufficiency:** There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients, compared to subjects with normal renal function. No dosage adjustment is therefore required in such patients (see WARNINGS AND PRECAUTIONS, Renal, and DOSING AND ADMINISTRATION, Dosing Considerations). Since metformin is contraindicated in patients

with renal impairment, metformin in combination with TEVA-ROSIGLITAZONE is contraindicated in these patients.

## STORAGE AND STABILITY

Store at controlled room temperature 15ºC to 30ºC.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-ROSIGLITAZONE tablets contain rosiglitazone maleate equivalent to 2, 4 or 8 mg rosiglitazone.

Each pentagonal film-coated tablet contains rosiglitazone as the maleate as follows:

TEVA-ROSIGLITAZONE 2 mg: pink pentagonal shaped tablet with "rph" engraved on one side and "2 mg" on the other side. Available in blisters of 30 (3 strips of 10 tablets) and bottles of 100 and 500.

TEVA-ROSIGLITAZONE 4 mg: brown pentagonal shaped tablet with "rph" engraved on one side and "4 mg" on the other side. Available in blisters of 30 (3 strips of 10 tablets) and bottles of 100 and 500.

TEVA-ROSIGLITAZONE 8 mg: red-brown pentagonal shaped tablet with "rph" engraved on one side and "8 mg" on the other side. Available in blisters of 30 (3 strips of 10 tablets) and bottles of 100 and 500.

Hydroxyl propyl methyl cellulose, Iron oxide red, lactose D80, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, talc, titanium dioxide and triacetin.

In addition each strength contains the following ingredients: **2 mg:** Indigo Carmne Aluminum Lake, **4 mg:** iron oxide yellow and **8 mg:** iron oxide yellow and iron oxide black.

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

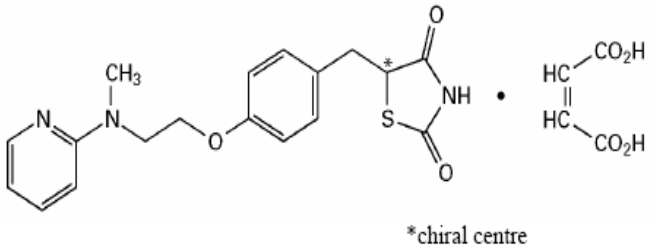
Proper name: rosiglitazone maleate

Chemical name: (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl] -2,4-thiazolidinedione, (Z)-2-butenedioate (1:1)

Molecular formula: $C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$

Molecular mass: 473.51(357.44 free base)

Structural formula:




*chiral centre

Physicochemical properties:

| | |
|---|---|
| Physical Description: | A white to off-white solid. |
| Solubility: | Readily soluble in ethanol and buffered aqueous solution with pH 2.3; solubility decreases with increasing pH in the physiological range. |
| pH: | pH value of a saturated solution of rosiglitazone maleate in water is 3.3, and in 0.9% saline is 3.4. |
| pKa: | pKa1=6.1, pKa2=6.8 |
| Partition Coefficient: | The distribution coefficient of rosiglitazone maleate, was measured by the shake-flask method, using a pH 6.5 phosphate buffer. In n-octanol/water the distribution coefficient was determined to be 194 (logD = +2.29). In cyclohexane/water the distribution coefficient was determined to be 0.32 (logD = - 0.49). |
| Melting Point: | Range of 122°C to 123°C |

## CLINICAL TRIALS

Comparative Bioavailability Study

A single dose crossover comparative bioavailability study of TEVA-ROSIGLITAZONE 8 mg tablets and Avandia® 8 mg tablets following an 8 mg dose in 21 healthy male volunteers under fasting conditions was conducted. The results indicate that TEVA-ROSIGLITAZONE 8 mg tablets are bioequivalent to Avandia® 8 mg tablets. The summary of results is presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

| Rosiglitazone (1 x 8 mg) From measured data Geometric LS Mean[1] Arithmetic Mean (CV %) | | | | |
|---|---|---|---|---|
| Parameter | TEVA-ROSIGLITAZONE * | Avandia®† | % Ratio of Geometric Means | 90% Confidence Interval (%) |
| $AUC_T$ (ng*h/mL) | 2853.94<br>2893.26 (18.01) | 2712.02<br>2738.97 (13.77) | 105.23 | 101.02 - 109.62 |
| $AUC_I$ (ng*h/mL) | 3078.88<br>3136.06 (21.14) | 2905.12<br>2941.16 (15.60) | 105.98 | 101.05 - 111.15 |
| $C_{max}$ (ng/mL) | 646.33<br>652.29 (13.24) | 627.64<br>630.81 (11.35) | 102.98 | 96.74 - 109.61 |
| $T_{max}$§ (h) | 0.75<br>(0.33 - 1.75) | 0.75<br>(0.333 - 1.25) | | |
| $T_{½}$€ (h) | 3.60 (15.02) | 3.51 (12.62) | | |

* TEVA-ROSIGLITAZONE 8 mg tablets (Teva Canada Limited).
† Avandia® 8 mg tablets (GlaxoSmithKline (Canada) Inc.) were purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only
[1] Geometric least-squares means are presented for unbalanced study

### Monotherapy

A total of 2315 patients with type 2 diabetes, previously treated with diet alone or antidiabetic medication(s), were treated with rosiglitazone maleate as monotherapy in six double-blind studies, which included two 26-week placebo-controlled studies, one 52-week glyburide-controlled study, and three placebo-controlled dose-ranging studies of 8 to 12 weeks duration. Previous antidiabetic medication(s) were withdrawn and patients entered a 2 to 4 week placebo run-in period prior to randomization.

Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes with inadequate glycemic control (mean baseline FPG approximately 12.7 mmol/L and mean baseline A1C 0.089), were conducted. Treatment with rosiglitazone maleate produced statistically significant improvements in FPG and A1C compared to baseline and relative to placebo (Table 6).

**Table 6: Glycemic Parameters in Two 26-Week Placebo-Controlled Trials**

| **Study A** | **Placebo** | **Rosiglitazone Maleate 2mg twice daily** | **Rosiglitazone Maleate 4mg twice daily** |
|---|---|---|---|
| **N** | 158 | 166 | 169 |
| **FPG (mmol/L)** | | | |
| Baseline (mean) | 12.7 | 12.6 | 12.2 |
| Change from baseline (mean) | 1.1 | -2.1 | -3 |
| Difference from placebo (adjusted mean) | | -3.2* | -4.2* |
| Responders (≥ 1.7 mmol/L decrease from baseline) | 16% | 54% | 64% |
| **A1C (ratio)** | 0.09 | 0.09 | 0.088 |
| **Baseline (mean)** | 0.009 | -0.003 | -0.006 |
| **Change from baseline (mean)** | | -0.012* | -0.015* |
| **Responders (≥ 0.007 decrease in ratio from baseline)** | 6% | 40% | 42% |

| **Study B** | **Placebo** | **Rosiglitazone Maleate 4mg once daily** | **Rosiglitazone Maleate 2mg twice daily** | **Rosiglitazone Maleate 8mg once daily** | **Rosiglitazone Maleate 4mg twice daily** |
|---|---|---|---|---|---|
| **N** | 173 | 180 | 186 | 181 | 187 |
| **FPG (mmol/L)** | | | | | |
| Baseline (mean) | 12.5 | 12.7 | 12.5 | 12.7 | 12.7 |
| Change from baseline (mean) | 0.4 | -1.4 | -1.9 | -2.3 | -3.1 |
| Difference from placebo (adjusted mean) | - | -1.7* | -2.4* | -2.7* | -3.4* |
| Responders (≥ 1.7 mmol/L decrease from baseline) | 19% | 45% | 54% | 58% | 70% |
| **A1C (ratio)** | | | | | |
| **Baseline (mean)** | 0.089 | 0.089 | 0.089 | 0.089 | 0.089 |
| **Change from baseline (mean)** | 0.008 | 0 | -0.001 | -0.003 | -0.007 |
| **Difference from placebo (adjusted mean)** | - | -0.008* | -0.009* | -0.011* | -0.015* |
| **Responders (≥ 0.007 decrease in ratio from baseline)** | 9% | 28% | 29% | 39% | 54% |

*<0.0001 compared to placebo

When administered at the same total daily dose, rosiglitazone maleate was generally more effective in reducing FPG and A1C when administered in divided doses twice daily compared to once daily doses. However, for A1C, the difference between the 4 mg once daily and 2 mg twice daily doses was not statistically significant.

The study populations included patients who were not previously treated with antidiabetic medication (diet only patients) and those who were previously treated with antidiabetic medications (a single agent or a combination of agents) at the time of study enrollment. All patients entered a 6-8 week wash out/run-in period prior to randomization into the 26 week double-blind treatment phase. During the run-in period, patients received diabetic diet instructions/reinforcement plus placebo. The A1C data for the diet only patients and the previously treated patients are provided in Table 7.

**Table 7: A1C (ratio) by Prior Therapy in Two 26- Week Placebo Controlled Trials (Pooled Data)**

| | Placebo | Rosiglitazone Maleate 4 mg once daily | Rosiglitazone Maleate 2 mg twice daily | Rosiglitazone Maleate 8 mg once daily | Rosiglitazone Maleate 4 mg twice daily |
|---|---|---|---|---|---|
| **Diet only** | | | | | |
| **N** | 84 | 40 | 90 | 53 | 92 |
| Screening (mean) | 0.089 | 0.089 | 0.090* | 0.089* | 0.090* |
| Baseline (mean) | 0.085 | 0.085 | 0.088 | 0.086 | 0.086 |
| Week 26 (mean) | 0.089 | 0.076 | 0.079 | 0.078 | 0.076 |
| Change from baseline (mean) | 0.004 | -0.009 | -0.009 | -0.008 | -0.010 |
| Difference from placebo (adjusted mean) | | -0.012 | -0.012 | -0.011 | -0.014 |
| **Prior Single Agent** | | | | | |
| **N** | 208 | 111 | 218 | 99 | 232 |
| Screening (mean) | 0.084 | 0.082 | 0.082 | 0.083 | 0.082* |
| Baseline (mean) | 0.091 | 0.088 | 0.089 | 0.090 | 0.090 |
| Week 26 (mean) | 0.101 | 0.089 | 0.088 | 0.087 | 0.084 |
| Change from baseline (mean) | 0.010 | 0.001 | -0.001 | -0.003 | -0.005 |
| Difference from placebo (adjusted mean) | | -0.009 | -0.011 | -0.013 | -0.016 |
| **Prior Multiple Agents** | | | | | |
| **N** | 39 | 29 | 44 | 29 | 32 |
| Screening (mean) | 0.083 | 0.087** | 0.080 | 0.080 | 0.082 |
| Baseline (mean) | 0.096 | 0.100** | 0.096 | 0.093 | 0.094 |
| Week 26 (mean) | 0.105 | 0.107 | 0.100 | 0.097 | 0.093 |
| Change from baseline (mean) | 0.009 | 0.007 | 0.004 | 0.004 | -0.001 |
| Difference from placebo (adjusted mean) | | -0.000 | -0.004 | -0.004 | -0.011 |

*mean based on (N-1) patients
** mean based on (N+1) patients

In a 24 week, double-blind study, patients with type 2 diabetes which was poorly controlled on diet and exercise alone (mean baseline A1C 0.114) received rosiglitazone maleate 4 mg once daily or 8 mg once daily. Statistically significant improvements in A1C compared to baseline were observed for rosiglitazone maleate mg and 8 mg (mean reduction of 0.015 and 0.025, respectively). Statistically significant improvements in FPG compared to baseline were also observed for rosiglitazone maleate 4 mg and 8 mg (mean reduction of 2.60 mmol/L and 4.74 mmol/L, respectively). The reduction from baseline in A1C and the reduction from baseline in FPG were significantly greater with 8 mg of rosiglitazone maleate compared to 4 mg of rosiglitazone maleate.

## Long Term Studies:

Long-term maintenance of effect was evaluated in a 52-week, double-blind, glyburide-controlled trial in patients with type 2 diabetes. Patients were randomized to treatment with rosiglitazone

maleate 2 mg twice daily (N=195) or rosiglitazone maleate 4 mg twice daily (N=189) or glyburide (N=202) for 52 weeks. Patients receiving glyburide were given an initial dosage of either 2.5 mg/day or 5.0 mg/day. The dosage was then titrated in 2.5 mg/day increments over the next 12 weeks, to a maximum dosage of 15.0 mg/day in order to optimize glycemic control. Thereafter the glyburide dose was kept constant. The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a statistically significant improvement in glycemic control from baseline (Figures 1 and 2). At the end of week 52, the reduction from baseline in FPG and A1C was -2.26 mmol/L and -0.0053 with rosiglitazone maleate 4 mg twice daily; -1.41 mmol/L and -0.0027 with rosiglitazone maleate 2 mg twice daily; and -1.67 mmol/L and -0.0072 with glyburide. For A1C, the difference between rosiglitazone maleate 4 mg twice daily and glyburide was not statistically significant at week 52. The initial fall in FPG with glyburide was greater than with rosiglitazone maleate; however, this effect was less durable over time. The improvement in glycemic control seen with rosiglitazone maleate 4 mg twice daily at week 26 was maintained through week 52 of the study.

**Figure 1: Mean FPG Over Time in a 52-Week Glyburide-Controlled Study**

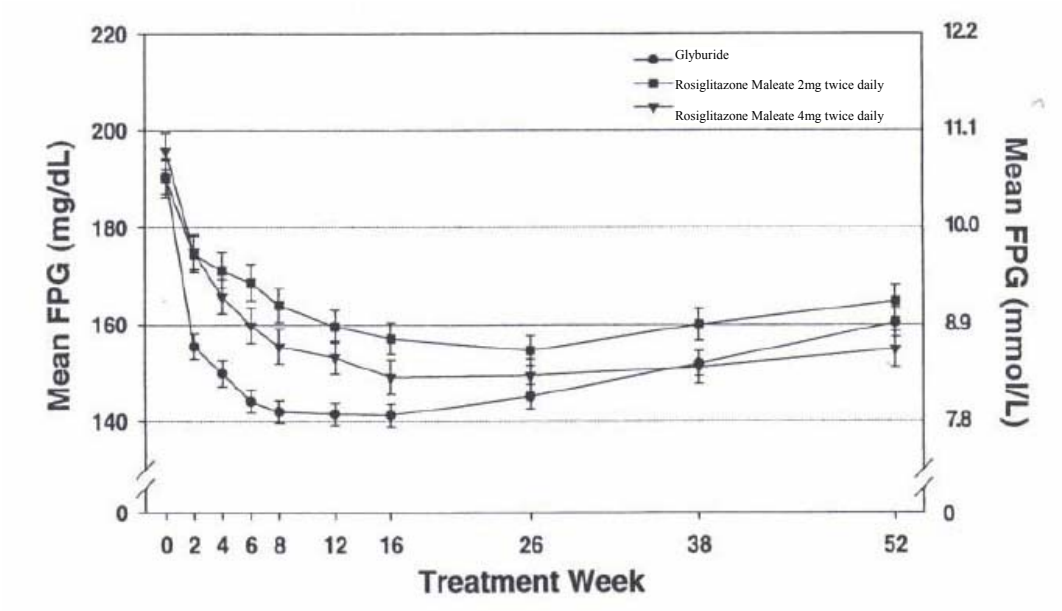
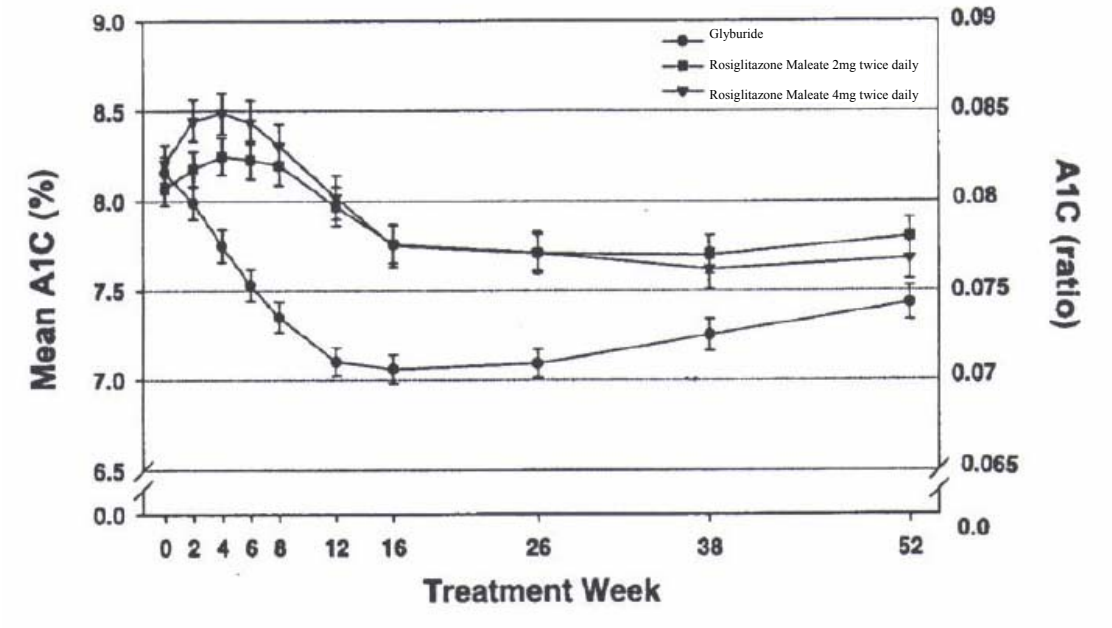



**Figure 2: Mean A1C Over Time in a 52-Week Glyburide-Controlled Study**



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

In a 52-week open-label safety study comparing rosiglitazone maleate 4 mg twice daily (n=104) with glyburide (n=99), treatment with rosiglitazone maleate resulted in a significant decrease from baseline in 24-hour ambulatory diastolic blood pressure compared to both baseline and glyburide, with no change from baseline in systolic blood pressure. In patients treated with rosiglitazone maleate, there was a decrease in fasting immunoreactive insulin (-8.6 pmol/L) from a baseline value of 118.0 pmol/L. In patients treated with glyburide, there was an increase in insulin (34.9 pmol/L) from a baseline value of 104.3 pmol/L. Fifty-two weeks treatment with rosiglitazone maleate 4 mg twice daily was associated with a 54 percent reduction in microalbuminuria, compared to a 25 percent reduction during treatment with glyburide. A greater proportion of patients treated with rosiglitazone normalized urinary albumin excretion (43%) compared to glyburide (6%) at 52 weeks. Few patients with normal albumin excretion progressed on therapy with either agent. Likewise, in two double-blind, placebo controlled trials, 26 weeks treatment with rosiglitazone maleate in patients with microalbuminuria resulted in reductions in urinary albumin excretion ranging 28 to 42 percent, compared with reductions of 13 to 22 percent during placebo treatment.

Open-labelled extension studies to rosiglitazone monotherapy double-blind, placebo-controlled trials showed a decrease in baseline A1C levels from 0.086 in the 4 mg bd group and 0.085 in the 8 mg od group to 0.074 and 0.073, respectively, at month 36. In addition, FPG open-labelled baseline values decreased from 10.19 mmol/L in the 4 mg bd group and 10.13 mmol/L in the 8 mg od group to 7.77 mmol/L and 7.71 mmol/L, respectively, at month 36. Figures 3, 4, 5 and 6 show that the decreases in mean A1C and FPG values achieved during the treatment months were sustained in those patients who remained in the study.

**Figure 3: Mean A1C Over Time**

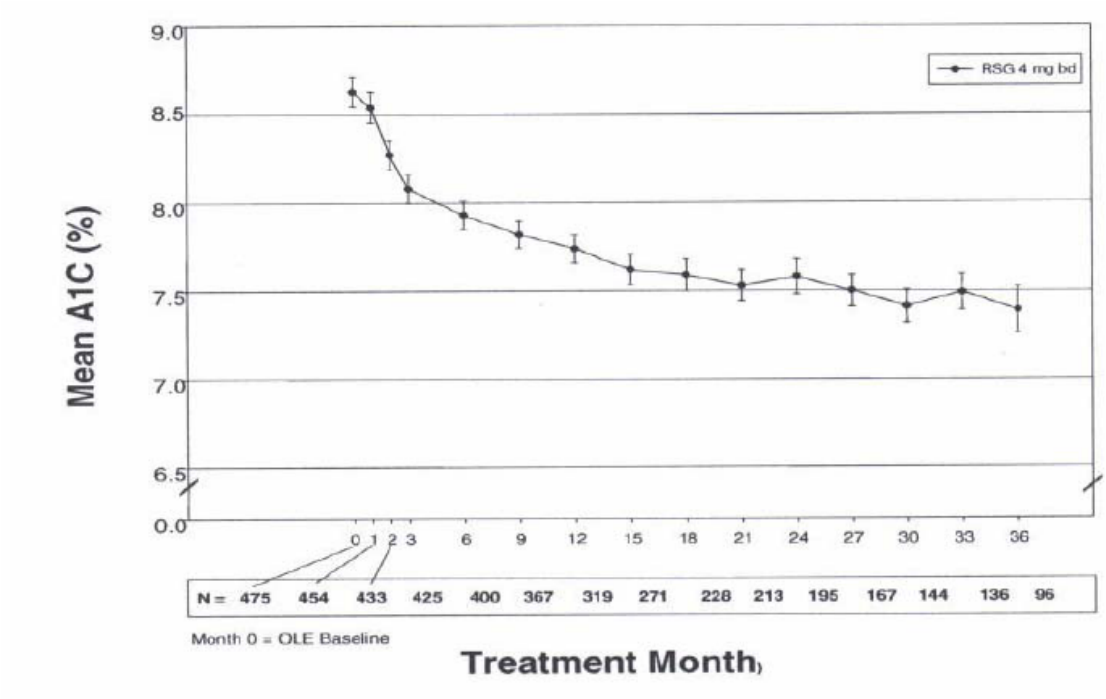



**Figure 4: Mean A1C Over Time**

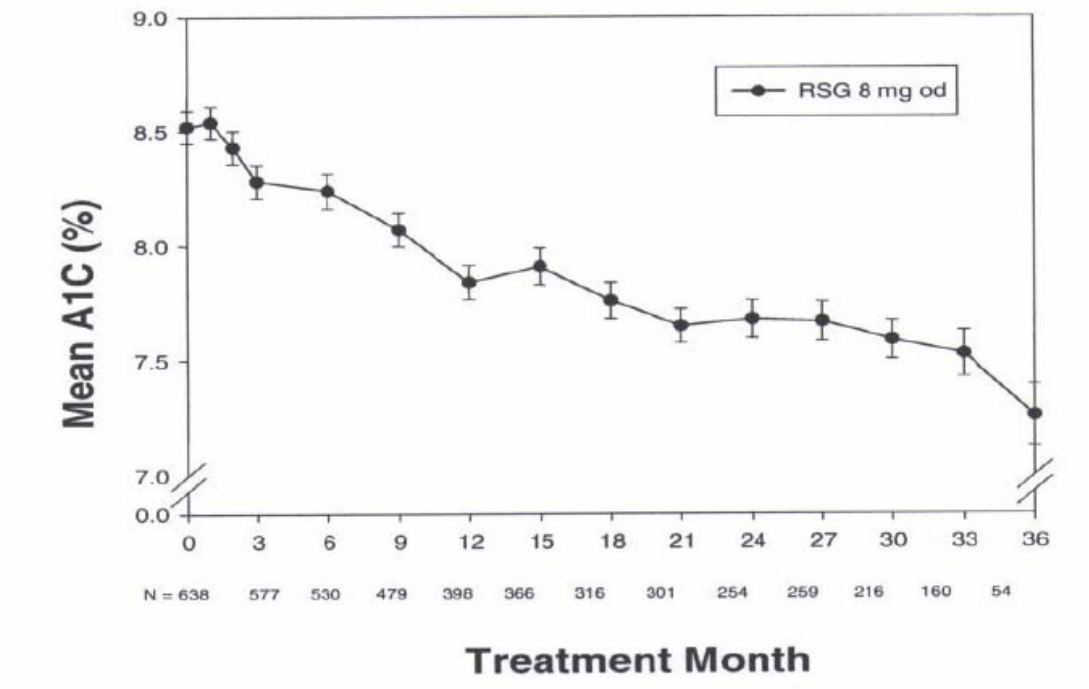


**Figure 5: Mean FPG Over Time**

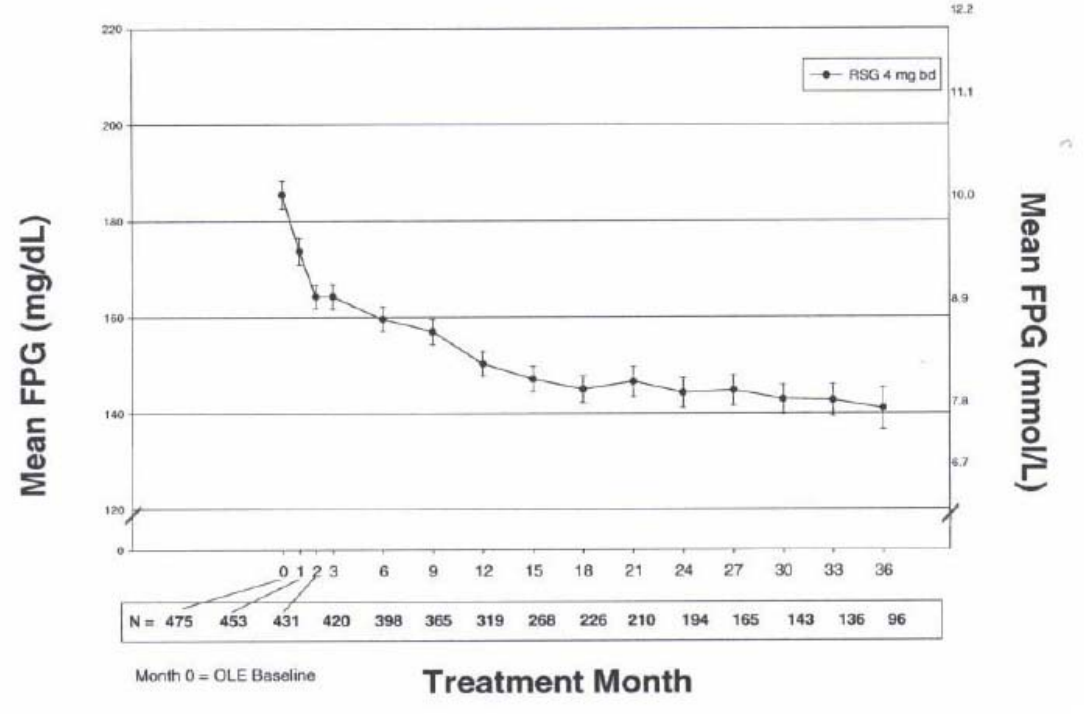
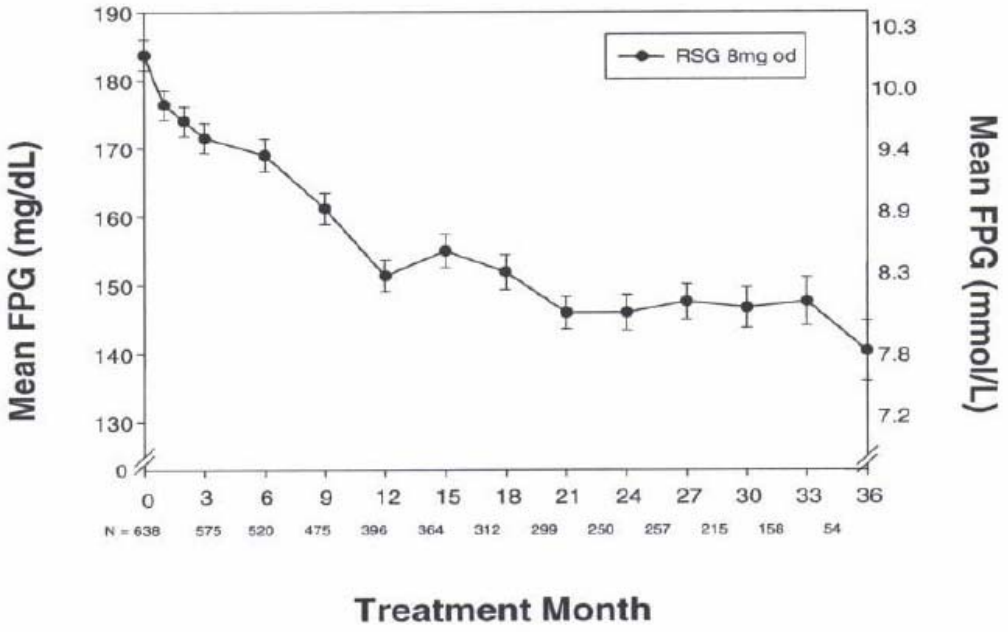



**Figure 6: Mean FPG Over Time**




A Diabetes Outcome Progression Trial (ADOPT) was a multicenter, double-blind, controlled trial (n = 4,351) with a treatment duration of 4-6 years (median duration of 4 years) to compare the efficacy and safety of rosiglitazone maleate, metformin, and glyburide monotherapy in patients recently diagnosed with type 2 diabetes mellitus (≤3 years) inadequately controlled with diet and exercise. The mean age of patients was 57 years and the majority of patients (83%) had no known

history of cardiovascular disease. The mean baseline FPG and A1C were 8.4 mmol/L and 7.4% respectively. Patients were randomized to receive either rosiglitazone maleate 4 mg once daily, metformin hydrochloride 500 mg once daily, or glyburide 2.5 mg once daily, and doses were titrated to optimal glycemic control up to a maximum of 4 mg twice daily for rosiglitazone maleate, 1,000 mg twice daily for metformin hydrochloride, and 7.5 mg twice daily for glyburide. The primary efficacy outcome was time to monotherapy failure, defined either as an FPG>10.0 mmol/L on consecutive occasions following at least 6 weeks of treatment at the maximum tolerated dose of study medication or hyperglycemia deemed to be monotherapy failure by an independent adjudication committee. The withdrawal rate due to reasons other than monotherapy failure was 43%, 47%, and 41% for rosiglitazone maleate, metformin, and glyburide treatment groups, respectively.

At 5 years, only 20% of the original cohort was being followed. The cumulative incidence (95% CI) of monotherapy failure at 5 years was 15% (0.12, 0.17) with rosiglitazone maleate, 21% (0.18, 0.24) with metformin, and 34% (0.30, 0.37) with glyburide (hazard ratio 0.68 [95% CI 0.55, 0.85] versus metformin, HR 0.37 [95% CI 0.30, 0.45] versus glyburide).

Fractures were reported in a greater number of females with rosiglitazone maleate compared to glyburide or metformin (see WARNINGS AND PRECAUTIONS, Fractures and Adverse Drug Reaction Overview). Otherwise, adverse reactions observed with rosiglitazone maleate were generally consistent to those observed in shorter-term trials. Rosiglitazone maleate monotherapy was associated with weight gain (see Adverse Drug Reaction Overview), edema, increased levels of LDL cholesterol and a reduction in the hematocrit. Metformin was associated with gastrointestinal side effects. Glyburide was associated with hypoglycemia and lesser weight gain. There was an increase in use of statins and loop diuretics in the rosiglitazone maleate arm. The myocardial ischemic event rate observed was similar among patients on rosiglitazone maleate, metformin and glyburide.

**Cardiovascular Studies:**
Two echocardiography studies in type 2 diabetic patients (a 52-week study with rosiglitazone maleate 4 mg twice daily and a 26-week study with 8 mg once daily), designed to detect a change in left ventricular mass of 10% or more, showed no deleterious alteration in cardiac structure or function. Compared to placebo, there was a small, statistically significant increase in median plasma volume (1.8 mL/kg) in healthy volunteers treated with rosiglitazone maleate 8 mg once daily for 8 weeks.

Patients with congestive heart failure (CHF) New York Heart Association (NYHA) Class I and II treated with rosiglitazone maleate have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-controlled echocardiographic study 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 maleate treatment compared to placebo during the 52-week study (see Table ~~7~~ 8).

**Table 8: Emergent Cardiovascular Adverse Events in Patients with Congestive Heart Failure (NYHA Class I and II) treated with Rosiglitazone Maleate or Placebo (in addition to Background Antidiabetic and CHF Therapy)**

| Events | Placebo | Rosiglitazone Maleate |
|---|---|---|
| | N = 114<br>n (%) | N = 110<br>n (%) |
| **Adjudicated** | | |
| Cardiovascular Deaths | 4 (4) | 5 (5) |
| CHF Worsening<br>With overnight hospitalization<br>Without overnight hospitalization | 4 (4)<br>4 (4)<br>0 (0) | 7 (6)<br>5 (5)<br>2 (2) |
| New or Worsening Edema | 10 (9) | 28 (25) |
| New or Worsening Dyspnea | 19 (17) | 29 (26) |
| Increases in CHF Medication | 20 (18) | 36 (33) |
| Cardiovascular Hospitalization* | 15 (13) | 21 (19) |
| **Investigator-reported, Non-adjudicated** | | |
| Ischemic Adverse Events<br>Myocardial Infarction<br>Angina | 5 (4)<br>2(2)<br>3(3) | 10 (9)<br>5(5)<br>6(5) |

*Includes hospitalization for any cardiovascular reason

## Combination with Metformin

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

In one study, patients inadequately controlled on 2.5 g/day of metformin (mean baseline FPG 12.0 mmol/L and mean baseline A1C 0.088) were randomized to receive rosiglitazone maleate 4 mg once daily, rosiglitazone maleate 8 mg once daily, or placebo in addition to metformin. A statistically significant improvement in FPG and A1C was observed in patients treated with the combinations of metformin and rosiglitazone maleate 4 mg once daily and rosiglitazone maleate 8 mg once daily, versus patients continued on metformin alone (Table 9).

**Table 9: Glycemic Parameters in a 26-Week Combination Study**

| | Metformin | Rosiglitazone maleate 4mg once daily + metformin | Rosiglitazone maleate 8 mg once daily + metformin |
|---|---|---|---|
| **N** | 113 | 116 | 110 |
| **FPG (mmol/L)** | | | |
| Baseline (mean) | 11.9 | 11.9 | 12.2 |
| Change from baseline (mean) | 0.3 | -1.8 | -2.7 |
| Difference from metformin alone (adjusted mean) | | -2.2* | -2.9* |
| Responders (≥ 1.7 mmol/L decrease from baseline) | 20% | 45% | 61% |

| | Metformin | Rosiglitazone maleate 4mg once daily + metformin | Rosiglitazone maleate 8 mg once daily + metformin |
|---|---|---|---|
| **A1C (ratio)** | | | |
| Baseline (mean) | 0.086 | 0.089 | 0.089 |
| Change from baseline (mean) | 0.005 | -0.006 | -0.008 |
| Difference from metformin alone (adjusted mean) | | -0.010* | -0.012* |
| Responders (≥ 0.007 decrease in ratio from baseline) | 11% | 45% | 52% |

*<0.0001 compared to metformin

In a second 26-week study, patients with type 2 diabetes inadequately controlled on 2.5 grams/day of metformin who were randomized to receive the combination of rosiglitazone maleate 4 mg twice daily and metformin (N=105) showed a statistically significant improvement in glycemic control with a mean treatment effect for FPG of -3.1 mmol/L and a mean treatment effect for A1C of -0.008 over metformin alone. The combination of metformin and rosiglitazone maleate resulted in lower levels of FPG and A1C than either agent alone.

Patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin and who were switched to monotherapy with rosiglitazone maleate demonstrated loss of glycemic control, as evidenced by increases in FPG and A1C. In this group, increases in LDL and VLDL were also seen.

In a third 24 week double blind study, the efficacy of rosiglitazone in combination with 1.0 gram/day of metformin hydrochloride was compared with continued titration to 2.0 grams/day of metformin hydrochloride. Patients with type 2 diabetes inadequately controlled on 1.0 gram/day of metformin hydrochloride were randomized to receive rosiglitazone 4 mg twice daily in addition to metformin 1.0 gram/day or to receive 2.0 grams/day of metformin monotherapy. Patients receiving rosiglitazone received an initial dose of 2 mg twice daily for 8 weeks, followed by 4 mg twice daily for the remainder of the study. Patients receiving metformin monotherapy received 1.5 grams/day of metformin for 8 weeks, followed by 2.0 grams/day for the remainder of the study. At the end of week 24, the addition of rosiglitazone to 1.0 gram/day of metformin was at least as effective as 2.0 grams/day of metformin in improving A1C (mean reduction of A1C of 0.0093 and 0.0071, respectively). At the end of week 24, the reduction from baseline in FPG was significantly greater with rosiglitazone added to 1.0 gram/day (mean reduction of 2.29 mmol/L) compared to 2.0 grams/day of metformin (mean reduction of 1.12 mmol/L). Significantly more patients receiving rosiglitazone plus 1.0 gram/day of metformin achieved a 0.007 or greater reduction from baseline in A1C (59.5%) compared to patients receiving 2.0 grams/day of metformin (49.5%) (p=0.0247).

**Long Term Studies:**
Open-labelled extension studies of rosiglitazone maleate in combination with metformin double-blind, placebo-controlled trials showed a decrease in baseline A1C levels from 0.087 in the 4 mg bd group and 0.084 in the 8 mg od group to 0.071 and 0.077 respectively at month 30. In addition, FPG open-labelled baseline values decreased from 10.52 mmol/L in the 4 mg bd group and 10.36 mmol/L in the 8 mg od group to 7.55 mmol/L and 8.28 mmol/L, respectively, at month 30. Figures 7 and 8 show that the decreases in mean A1C and mean FPG values achieved during the treatment months were sustained in those patients who remained in the study.

**Figure 7: Mean A1C Values Over Time**

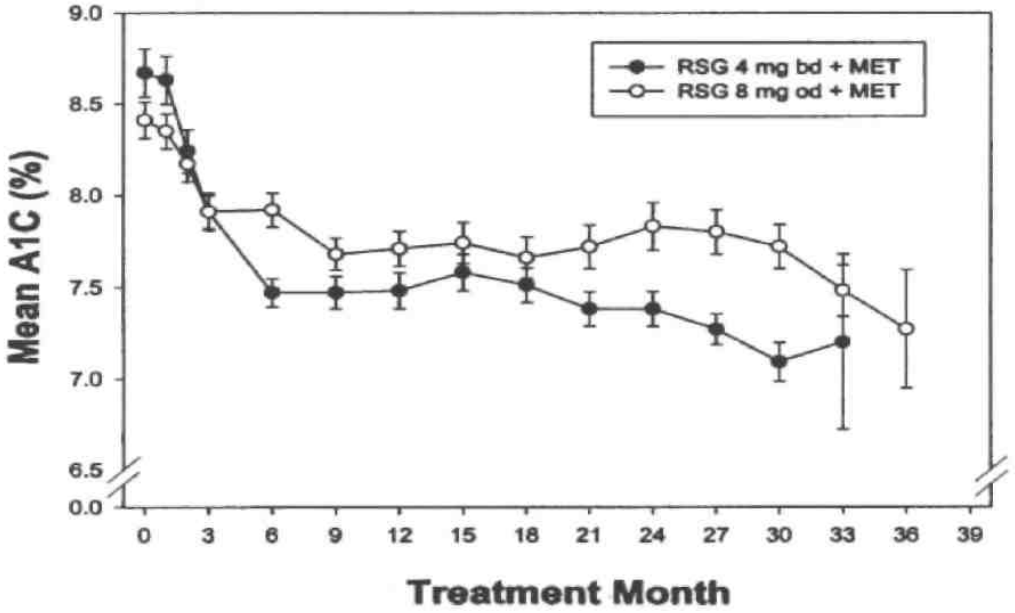
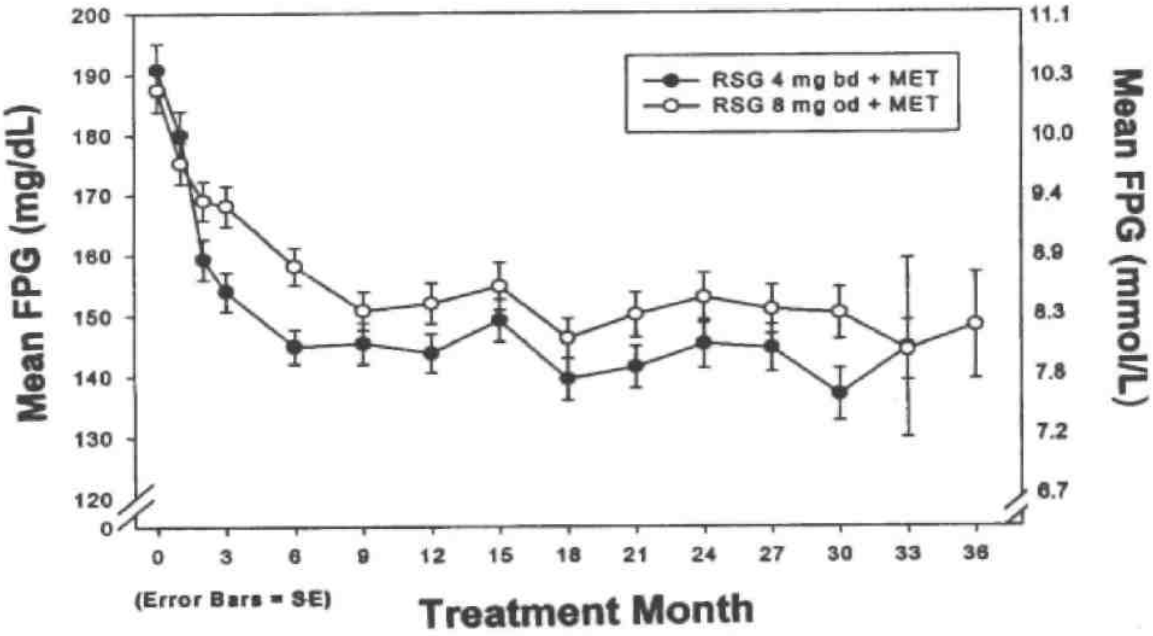



**Figure 8: Mean FPG Values Over Time**



**Combination with Sulfonylurea**

A total of 1028 patients with type 2 diabetes participated in three 26-week randomized, double-blind, placebo/active-controlled studies and one 2-year double-blind, active-controlled study in elderly patients designed to assess the efficacy and safety of rosiglitazone maleate in combination with sulfonylurea. Rosiglitazone maleate 2 mg or 4 mg daily, administered in either once daily or twice daily dosing regimens, was added to the therapy of patients who were inadequately controlled on a submaximal or maximal dose of sulfonylurea alone.

Across three 26-week studies, placebo plus sulfonylurea (n = 406) or rosiglitazone maleate 4 mg daily plus sulfonylurea (n = 397), was assessed in patients inadequately controlled on a sulfonylurea alone. Single or divided doses of rosiglitazone maleate 4 mg daily plus sulfonylurea significantly reduced FPG (mean reduction of 1.8 to 3.1 mmol/L) and A1C (mean reduction of 0.009 to 0.14) compared to placebo plus sulfonylurea (Table 9).

**Table 9: Glycemic Parameters in 26-week Double-blind Studies of RSG 4 mg + SU**

| | **Study C** | | **Study D** | | **Study E** | |
|---|---|---|---|---|---|---|
| | **SU** | **RSG+SU** | **SU** | **RSG+SU** | **SU** | **RSG+SU** |
| N | 192 | 183 | 115 | 116 | 99 | 98 |
| **FPG (mmol/L)** Baseline (mean) | 11.5 | 11.4 | 11.6 | 11.9 | 12.2 | 12.3 |
| Change from baseline (mean) | 0.3 | -2.1 | 1.3 | -1.4 | 1.3 | -1.7 |
| Difference from placebo (adjusted mean) | -- | -2.4* | -- | -2.6* | -- | -3.1* |
| Responders# (%) | 21% | 56% | 13% | 46% | 10% | 50% |
| N | 192 | 183 | 115 | 116 | 99 | 98 |
| **A1C (ratio)** Baseline (mean) | 0.09 | 0.092 | 0.09 | 0.0901 | 0.1 | 0.092 |
| Change from baseline (mean) | 0 | -0.009 | 0 | -0.003 | 0 | -0.01 |
| Difference from placebo (adjusted mean) | -- | -0.010* | -- | -0.009* | -- | -0.014* |
| Responders# (%) | 19% | 60% | 6% | 29% | 10% | 38% |

* $p < 0.0001$ compared to sulfonylurea

# Responders defined as A1C reduction $\geq 0.007$ or FPG reduction $\geq 1.7$ mmol/L

**Long Term Studies:**

In a long-term, randomized, double-blind study, 225 elderly type 2 diabetic patients (≥60 years of age) on half-maximal doses of sulfonylurea were randomized to either rosiglitazone maleate in addition to a half maximal dose of a sulfonylurea (glipizide) or uptitration of the sulfonylurea alone. Fifty-nine of 115 patients in the rosiglitazone maleate arm maintained glycemic control with rosiglitazone maleate 4 mg once daily plus glipizide 10 mg twice daily. In these 59 patients, the improvement of glycemic control was significant and durable over the 2-year study period (baseline mean A1C of 0.076 and week 104 mean A1C of 0.069).

In an open-labelled extension study it was observed that A1C values obtained during the double-blind studies could be maintained and further decreased with continued rosiglitazone treatment. A1C values decreased from 0.094 at open-label baseline to 0.079 at month 36 for those subjects that remained in the study (see Figure 9). Mean FPG values also decreased from open-label baseline, with the greatest decrease observed at month 36, for those subjects that remained in the study (see Figure 10).

**Figure 9: Mean A1C Over Time**

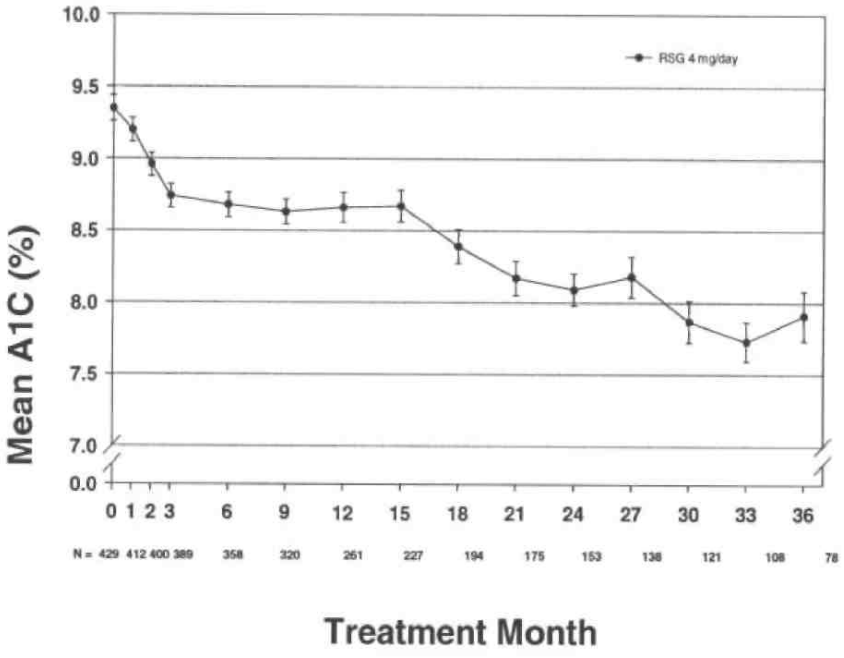
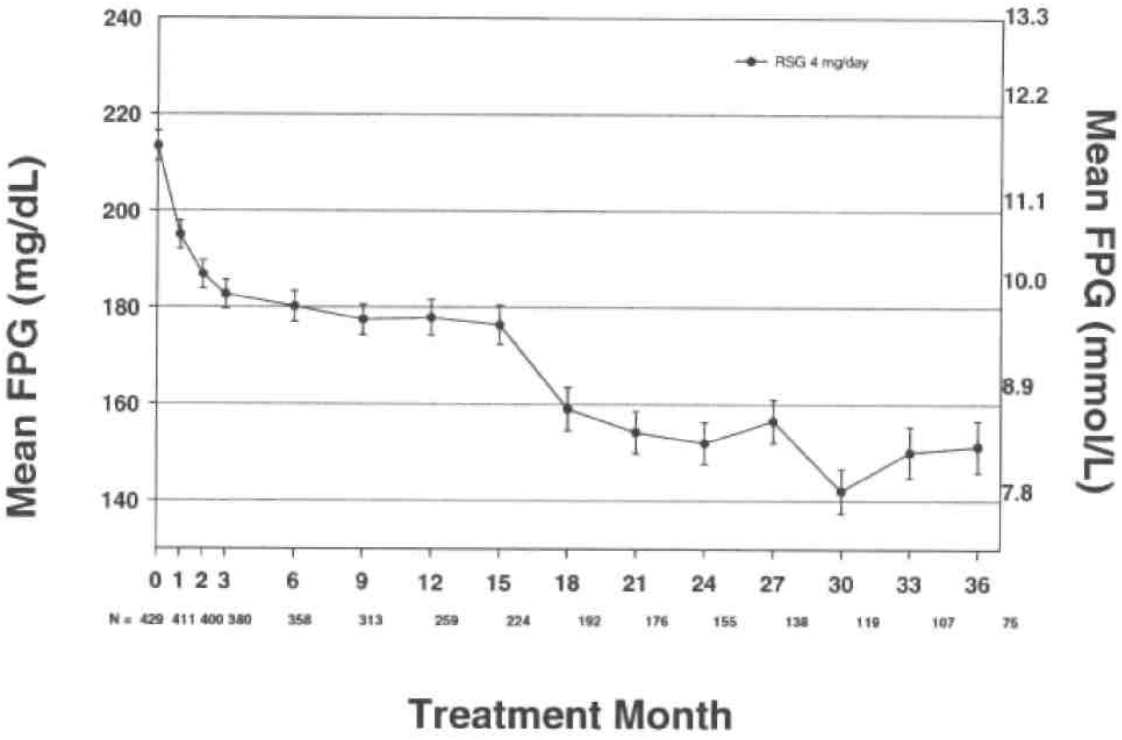



**Figure 10: Mean FPG Over Time**




**Combination with Insulin**

For safety reasons, the use of rosiglitazone in combination therapy with insulin is not indicated.

In two 26-week U.S. trials involving 611 patients with type 2 diabetes, rosiglitazone maleate plus insulin therapy was compared with insulin therapy alone. These trials included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions, including peripheral neuropathy (34%), retinopathy (19%), ischemic heart disease (14%), vascular disease (9%), and congestive heart failure (2.5%). In these clinical studies, an increased incidence of cardiac failure and other cardiovascular adverse events were seen in patients on rosiglitazone maleate and insulin combination therapy compared to insulin and placebo. Patients who experienced heart failure were on average older, had a longer duration of diabetes, and were mostly on the higher 8 mg daily dose of rosiglitazone maleate. In this population, however, it was not possible to determine specific risk factors that could be used to identify all patients at risk of heart failure on insulin combination therapy. Three of 10 patients who developed cardiac failure on insulin combination therapy during the double blind part of the fixed dose studies had no known prior evidence of congestive heart failure, or pre-existing cardiac condition.

In 26-week double-blind fixed dose studies, edema was reported with higher frequency in the rosiglitazone maleate plus insulin combination trials (insulin, 5.4%; and rosiglitazone maleate 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 maleate (see WARNINGS AND PRECAUTIONS, Cardiovascular). In these studies, approximately 2.5% of the patients were enrolled with a presenting medical condition of congestive heart failure (NYHA Class I/II). Patients with NYHA Class III and IV heart failure were excluded from all clinical trials.

Hypoglycemia was generally mild to moderate in nature and was dose-related when rosiglitazone was used in combination with insulin.

In the retrospective analysis of data from pooled clinical studies, a greater increased risk of myocardial ischemic events was observed in studies where rosiglitazone maleate was added to insulin.

## DETAILED PHARMACOLOGY

The antidiabetic activity of rosiglitazone has been demonstrated in a number of animal models of type 2 diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. Rosiglitazone normalizes blood glucose concentrations and reduces hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse and fa/fa fatty Zucker rat. Rosiglitazone also prevents the development of overt diabetes in both the db/db mouse and Zucker fa/fa Diabetic Fatty (ZDF) rat models. In addition, rosiglitazone prevents the development of systolic hypertension, proteinuria, renal morphologic abnormalities and renal dysfunction in the Zucker rat and prevents the deleterious changes in pancreatic morphology seen in untreated db/db mice, ZDF rats and Zucker fa/fa rats.

In animal models, rosiglitazone's antidiabetic activity was shown to be mediated by increased sensitivity to insulin's action in the liver, muscle and adipose tissues. 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.

## TOXICOLOGY

**Teratogenic Effects:**
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. Rosiglitazone caused placental pathology (labyrinth congestion and increased weight) in rats (≥ 3 mg/kg/day) but not in rabbits at 100 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 (AUC=11.94 μg.h/mL) in rats and 15 mg/kg/day (AUC=12.5 μg.h/mL) in rabbits.

**Impairment of Fertility:**
Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day. 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 with no such effects at 0.2 mg/kg/day (AUC=11.94 μg.h/mL). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day [AUCs of 8.21 and 44.14 μg.h/mL]) 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, apparently a thiazolidinedione class effect.

**Carcinogenesis and Mutagenesis:**
Two-year carcinogencity studies were conducted in Charles River CD-1 mice at doses of 0.4, 1.5 and 6 mg/kg/day in the diet and in Sprague-Dawley rats at oral gavage doses of 0.05, 0.3 and 2 mg/kg/day (top doses equivalent to approximately 10 to 20 times human AUC at the maximum recommended human dose of 8 mg/day). 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). 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). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue and appear to be rodent-specific.

Rosiglitazone was not mutagenic or clastogenic in the i*n 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 at toxic concentrations of 150 to 200 μg/mL, but this was regarded as system-specific with no general relevance.

**Cardiovascular-Renal:**
Heart weights were increased in mice (≥ 3 mg/kg/day), rats (≥ 5 mg/kg/day), and dogs (≥ 2 mg/kg/day) with rosiglitazone treatments. There were increases in wet and dry cardiac weight and total protein content. Morphometric analysis showed left ventricular hypertrophy, and echocardiographic assessments revealed an increase in left ventricular mass with a proportional increase in left ventricular wall area and lumen volume. The no-effect dose for cardiac hypertrophy was 0.5 mg/kg to 2 mg/kg among mice, rats and dogs in studies of up to 1 year duration.

In preclinical studies, thiazolidinediones cause plasma volume expansion and pre-load-induced cardiac hypertrophy. The cardiac hypertrophy was an adaptive consequence of an increase in preload, as shown by an increase in diastolic wall stress, with no contribution from afterload. The increase in preload derives from plasma volume expansion due to increased renal sodium and fluid retention in response to increased blood flow to specific tissues (particularly adipose, skin and gastrointestinal) and mild vasorelaxation.

**Liver:**
There was a small increase in liver weight in female rats (≥ 5 mg/kg/day) but no effects in male rats (40 mg/kg) or mice of either sex (20 mg/kg). Only in the dog were there increases in plasma enzyme activity (principally alanine aminotransferase, ALT) at doses of 0.5 mg/kg or greater. There was evidence of hepatocellular regeneration and oxidative stress in dogs with raised ALT. Species-specific hepatotoxicity in dogs may be attributed to toxic metabolites formed to a greater extent in this species rather than to parent drug exposure.

**Endocrine System:**
In rats only, ovary weight was decreased in association with a reduction/absence of corpora lutea at doses ≥ 5 mg/kg, and there was increased pituitary weight with lactotroph hyperplasia at doses ≥ 0.2 mg/kg. These changes in the ovary and pituitary of female rats were attributed to reduced ovarian synthesis of estradiol and progesterone to a greater extent, with a net increase in the ratio of plasma estradiol to progesterone concentrations. Whereas such changes in steroid hormone levels causing persistent vaginal estrus and lactotroph hyperplasia in female rats are sex and species-specific outcomes, lower levels of estradiol and progesterone in the cynomolgus monkey were associated with amenorrhea. The frequency of reports relating to menstrual dysfunction in clinical trials was low and similar to placebo (0.4% on rosiglitazone and placebo).

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**PART III: CONSUMER INFORMATION**

**TEVA-ROSIGLITAZONE**
rosiglitazone as rosiglitazone maleate

This leaflet is part III of a three-part "Product Monograph" for TEVA-ROSIGLITAZONE and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-ROSIGLITAZON . Contact your doctor or pharmacist if you have any questions about the drug.

Keep this leaflet until you have finished all your tablets as you may need to read it again.

## ABOUT THIS MEDICATION

What the medication is used for:
TEVA-ROSIGLITAZONE is a medicine used in addition to diet and exercise to lower blood sugar in patients with type 2 diabetes (non-insulin dependent) when all other diabetes medicines taken orally (by mouth) have not lowered blood sugar enough or are not appropriate.

TEVA-ROSIGLITAZONE may be used together with one of the following other diabetes medicines:
• metformin; or
• a sulfonylurea.

Before starting TEVA-ROSIGLITAZONE, your doctor will discuss the possible benefits and possible side effects of rosiglitazone to decide if rosiglitazone is right for you. Your doctor will ask you to read and sign a form indicating you understand the cardiovascular risks of TEVA-ROSIGLITAZONE.

In order for TEVA-ROSIGLITAZONE to be effective, you should continue to exercise and follow the diet recommended for your diabetes while taking TEVA-ROSIGLITAZONE .

People who have diabetes have problems with insulin. Insulin is produced by an organ called the pancreas (PAN-kree-us). Inside the pancreas are special cells called beta-cells that actually make insulin. Insulin is a hormone (body's own natural chemical) that allows the body's tissues to absorb glucose (known as "sugar") from the bloodstream to provide the body energy.

People with **Type 2 diabetes** do not make enough insulin, or the body tissues become less sensitive to insulin. When the tissues do not respond normally to insulin, it is as if they cannot "hear" the signals insulin sends out – this is called "insulin resistance."

With diabetes, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, heart disease, loss of limbs, and blindness. The main goal of treating diabetes is to lower your blood sugar to a normal level. Lowering and controlling blood sugar may help prevent or delay complications of diabetes such as heart disease, kidney disease or blindness.

**What it does:**
TEVA-ROSIGLITAZONE helps your body use its own insulin better by making the tissues more sensitive to insulin. The tissues are better able to "hear" the signals insulin sends out. That means the tissues will absorb sugar more easily, This in turn, keeps the amount of sugar in your blood at a more normal level.

**When it should not be used:**
- If you have or have had heart problems or heart failure (the heart cannot pump enough blood to the body's other organs), talk to your doctor. TEVA-ROSIGLITAZONE can cause your body to keep extra fluid (fluid retention), which can make some heart problems worse and lead to heart failure, swelling and weight gain.
- If you are allergic to TEVA-ROSIGLITAZONE or any of its components.
- If you have serious liver problems.
- If you are pregnant

What the medicinal ingredient is:
TEVA-ROSIGLITAZONE contain the active ingredient rosiglitazone maleate.

What the important nonmedicinal ingredients are:
Hydroxyl propyl methyl cellulose, iron oxide red, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, talc, titanium dioxide and triacetin.

In addition each strength contains the following ingredients:: **2 mg:** FD & C Blue #2/ Indigo Carmne Aluminum Lake, **4 mg:** iron oxide yellow and **8 mg:** iron oxide yellow and iron oxide black.

What dosage forms it comes in:
2 mg, 4 mg and 8 mg tablets

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**
Rosiglitazone maleate may increase the risk of serious heart problems, including:
- heart failure
- angina (chest pain)
- heart attack (myocardial infarction)
- fluid retention (with or without rapid weight gain)

TEVA-ROSIGLITAZONE should not be used if you have or have had heart problems.
**Before you use TEVA-ROSIGLITAZONE talk to your doctor about other options to treat your diabetes.**

BEFORE you use TEVA-ROSIGLITAZONE talk to your doctor or pharmacist about all your medical conditions, including if:
- you have experienced edema (swelling in the wrists, hands, feet or ankles)
- you have been diagnosed with angina (chest paint) or have had a heart attack
- you have heart-related risks, including cigarette smoking,

high blood pressure, high cholesterol, or a family history of heart attack
- you are taking nitrate medicines (such as nitroglycerin or isosorbide dinitrate).
- you have a type of diabetic eye disease called macular edema (swelling in the back of the eye).
- You have liver problems
- You are breastfeeding.
- You are pregnant or planning to become pregnant.
- you are not near menopause but not ovulating (e.g., you are a patient with polycystic ovary syndrome). TEVA-ROSIGLITAZONE could make you ovulate again, which means you could get pregnant. Talk to your doctor about birth control (e.g. hormonal contraceptive pills).

Broken bones, usually in the hand, upper arm or foot, have been seen in people taking TEVA-ROSIGLITAZONE. Talk to your doctor about the risk of fracture.

The safety and effectiveness of TEVA-ROSIGLITAZONE have not been established in children under 18 years of age, therefore rosiglitazone maleate should not be used in these patients.

TEVA-ROSIGLITAZONE is not recommended for type 1 diabetes or diabetic ketoacidosis (dangerously high levels of ketones, which signals the body doesn't have enough insulin).

TEVA-ROSIGLITAZONE is not approved for use with insulin therapy, therefore TEVA-ROSIGLITAZONE is not recommended for use with insulin.

TEVA-ROSIGLITAZONE is not approved for use with metformin AND a sulfonlurea, therefore TEVA-ROSIGLITAZONE is not recommended for use with metformin AND sulfonylurea.

## INTERACTIONS WITH THIS MEDICATION

TEVA-ROSIGLITAZONE may affect how other medicines work and some medicines may affect how TEVA-ROSIGLITAZONE works. Drugs that may interact with rosiglitazone maleate include: gemfibrozil (used to lower cholesterol and triglyceride levels in your blood) rifampin (used to treat tuberculosis), methrotrexate (used to treat psoriasis or rheumatoid arthritis).

Keep a list of all the medicines you take and tell your doctor and pharmacist about every medication you take. This means both prescription medications (the ones your doctor writes for you) and over-the-counter medications (the ones you buy in the drugstore, like cold or allergy medicines), or natural health products (herbal medicines).

## PROPER USE OF THIS MEDICATION

**Usual dose:**

The usual starting dose of TEVA-ROSIGLITAZONE is 4mg per day. Your doctor will decide on the dose of TEVA-ROSIGLITAZONE that is suitable for you.

TEVA-ROSIGLITAZONE should be taken by mouth once a day (in the morning) or twice a day (in the morning and in the evening) depending on the dose your doctor has given you. TEVA-ROSIGLITAZONE is a medicine that works over time. It may take anywhere from eight to twelve weeks to see the optimal effect.

Since food doesn't affect how your body uses TEVA-ROSIGLITAZONE, you can take it with meals or without. To help you remember to take TEVA-ROSIGLITAZONE, try to take it at the same time every day.

Test your blood sugar regularly as your doctor tells you.

**Remember: this medicine has been prescribed only for you. Do not give it to anybody else.**

Take your TEVA-ROSIGLITAZONE each day, as instructed by your doctor. TEVA-ROSIGLITAZONE can help control your blood sugar levels only if you take it regularly.

**Overdose:**

Taking too much of any medicine can be dangerous.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**

If you take TEVA-ROSIGLITAZONE **once a day** and miss one dose, take the dose as soon as you remember anytime during the day.

If you take TEVA-ROSIGLITAZONE **twice a day**, take the missed dose as soon as you remember. Then take the next dose at the usual time.

Never take three doses in one day to make up for a missed dose the day before.

If you **miss a whole day** of TEVA-ROSIGLITAZONE, just take your dose as usual the next day. Don't try to make it up by taking extra tablets.

**Recommended clinical and laboratory tests while taking TEVA-ROSIGLITAZONE**

Your doctor may do additional blood sugar tests to see how well TEVA-ROSIGLITAZONE is working.

Your doctor may also recommend a blood test to monitor your liver before you start TEVA-ROSIGLITAZONE and repeat the test periodically while you are on TEVA-ROSIGLITAZONE .

Your doctor should check your eyes regularly. Rarely, some patients have experienced vision changes due to swelling in the back of the eye while taking TEVA-ROSIGLITAZONE.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common side effects (could affect up to one in 10 people):
- Anemia (low red blood cell count) which may make you feel very weak or tired.
- Chest pain (angina)
- Heart failure or pulmonary edema (fluid accumulation in the lungs) when rosiglitazone is taken in combination with a sulfonylurea, or metformin. Symptoms of heart failure include shortness of breath, getting tired easily after light physical activity such as walking, unusual tiredness, waking up short of breath at night, swollen ankles or feet, and an unusually rapid increase in weight. Symptoms of fluid in the lungs are breathlessness, which may be very severe and usually worsens on lying down. Stop taking TEVA-ROSIGLITAZONE and call your doctor right away if you experience these symptoms.
- Edema (fluid retention or swelling) which could lead to or worsen heart failure. If you notice swelling in your extremities (arms and legs, hands and feet), an unusually rapid increase in weight, or if you experience unusual tiredness, trouble breathing or shortness of breath, call your doctor. These symptoms, although not specific, may signal heart problems or heart failure. Pay closer attention to these symptoms if you are using the higher dose of TEVA-ROSIGLITAZONE (8 mg) by itself or if you are using TEVA-ROSIGLITAZONE together with another diabetes medicine (e.g., a sulfonylurea) as fluid retention is more common.
- Broken bones usually in the hand, upper arm or foot in people taking rosiglitazone. Talk to your doctor about the risk of fracture.
- A small increase in total cholesterol levels. Total cholesterol is made up of "good cholesterol" (HDLc) and "bad cholesterol" (LDLc) and it is the balance of these that is more important than the total level. TEVA-ROSIGLITAZONE does not affect the balance of good and bad cholesterol. If you have any concerns about your cholesterol levels, you should speak to your doctor.
- Low blood sugar (hypoglycemia) if you are taking TEVA-ROSIGLITAZONE in combination with another diabetes medicine (e.g., metformin or a sulfonylurea). Dizziness, lack of energy, drowsiness, headache, trembling, sweating, 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 you feel that your symptoms of low blood sugar are uncomfortable. If you are using TEVA-ROSIGLITAZONE by itself, the risk of low blood sugar is low.
- Increased weight. Tell your doctor if you gain a lot of weight in a short period of time.

Uncommon side effects (could affect up to one in 100 people):
- Heart failure or pulmonary edema (fluid accumulation in the lungs) when TEVA-ROSIGLITAZONE is used alone. Symptoms of heart failure include shortness of breath, getting tired easily after light physical activity such as walking, waking up short of breath at night and swollen ankles or feet, and an unusually rapid increase in weight. Symptoms of fluid in the lungs are breathlessness, which may be very severe and usually worsens on lying down. Stop taking TEVA-ROSIGLITAZONE and call your doctor right away if you experience these symptoms.
- Constipation.
- Increased hunger.

Rare side effects (could affect up to one in 1,000 people):
- Liver problems. If you experience nausea, vomiting, stomach pain, lack of appetite, tiredness, dark urine, or yellowing of the skin, stop taking TEVA-ROSIGLITAZONE and call your doctor right away.
- Blurred vision due to swelling (or fluid) in the back of the eye.

Very rare side effects (could affect up to one in 10,000 people):
- Allergic reactions, which may include hives or rash (which may be itchy), or more serious symptoms which may occur suddenly, such as swelling of the face, lips, mouth, tongue or throat (which may cause difficulty in swallowing or breathing). Stop taking TEVA-ROSIGLITAZONE and call your doctor right away if you experience these symptoms.
- Breakthrough bleeding (unexpected vaginal bleeding or spotting) while using oral contraceptives, or generally, if you experience any symptoms that persist or become troublesome, these should be discussed with your doctor.

You may experience swelling of the parotid gland (salivary glands located over the jaw, in front of the ears).

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

| Symptom / effect | | Talk with your doctor | | Stop taking TEVA-ROSIGLITAZONE and call your doctor immediately |
|---|---|---|---|---|
| | | Only if severe | In all Cases | |
| **Common** | Low red blood cell count (anemia); feeling very weak or tired. | | ✓ | |

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| Symptom / effect | | Talk with your doctor | | Stop taking TEVA-ROSIGLITAZONE and call your doctor immediately |
| | | Only if severe | In all Cases | |
| **Common** | Fluid retention or swelling in extremities (arms and legs, hands and feet) without signs of heart failure or fluids in the lungs (see below). | | ✓ | |
| **Common** (when rosiglitazone maleate is taken with other antidiabetic medicines) | Low blood sugar levels (hypoglycaemi): Dizziness, lack of energy, drowsiness, headache, trembling sweating, or hunger | ✓ | | |

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| Symptom / effect | | Talk with your doctor | | Stop taking TEVA-ROSIGLITAZONE and call your doctor immediately |
| | | Only if severe | In all Cases | |
| ~~**Uncommon**~~ **Common** (Rosiglitazone maleate is taken in combination with a sulfonylurea or metformin) | Heart failure or fluid in the lungs (pulmonary edema): trouble breathing or shortness of breath, getting tired easily after light physical activity, unusual tiredness, waking up short of breath at night, an unusually rapid increase in weight. Fluid may also cause swollen ankles or feet. | | | ✓ |
| **Common** | Chest pain (angina) | | ✓ | |

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| Symptom / effect | | Talk with your doctor | | Stop taking TEVA-ROSIGLITAZONE and call your doctor immediately |
| | | Only if severe | In all Cases | |
| **Uncommon**<br><br>(when Rosiglitazone maleate is taken alone | Heart failure or fluid in the lungs (pulmonary edema); trouble breathing or shortness of breath, getting tired easily after light physical activity, unusual tiredness, waking up short of breath at night, an unusually rapid increase in weight Fluid may also cause swollen ankles or feet. | | | ✓ |
| **Rare** | Liver problems: nausea, vomiting, stomach pain, lack of appetite, tiredness, dark urine, or yellowing of the skin | | | ✓ |
| **Rare** | Blurred vision or decreased vision [which may be due to swelling (or fluid) in the back of the eye] | | | ✓ |

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| Symptom / effect | | Talk with your doctor | | Stop taking TEVA-ROSIGLITAZONE and call your doctor immediately |
| | | Only if severe | In all Cases | |
| **Very rare** | Allergic reactions: hives or rash (which may be itchy), or more serious symptoms which may occur suddenly, such as swelling of the face, lips, mouth. Tongue or throat (may cause difficulty in swallowing or breathing) | | | ✓ |

*This is not a complete list of side effects. For any unexpected effects while taking TEVA-ROSIGLITAZONE, contact your doctor or pharmacist.*

## HOW TO STORE IT

Store TEVA-ROSIGLITAZONE at room temperature (15ºC to 30ºC) out of the reach of children.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at: 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
-Fax toll-free to 1-866-678-6789, or
-Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect Canada Web site at:

***NOTE: Should you require information related to the management of the side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Teva Canada Limited, at:
1-800-268-4127 ext. 5005 (**English**)
1-877-777-9117 (**French**)
druginfo@tevacanada.com

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