PRODUCT MONOGRAPH

# Pr AVANDIA

rosiglitazone (as rosiglitazone maleate)

2 mg, 4 mg and 8 mg Tablets

Professed Standard

Antidiabetic Agent

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4

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## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Oral | Tablet /<br>2 mg, 4 mg and 8 mg | lactose monohydrate<br>*For a complete listing see Dosage Forms, Composition and Packaging section.* |

### INDICATIONS AND CLINICAL USE

AVANDIA (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 AVANDIA, physicians must:
- Document the eligibility of patients to meet the above criteria;
- Counsel each patient on the risks and benefits of AVANDIA, including the cardiovascular risks; and
- Obtain the patient's written informed consent to take the drug.

In combination therapy, AVANDIA 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 AVANDIA, 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, AVANDIA is not indicated in patients younger than 18 years of age. See WARNINGS AND PRECAUTIONS, Special Populations.

## CONTRAINDICATIONS

AVANDIA 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**

- AVANDIA, like other thiazolidinediones, can cause or exacerbate fluid retention and congestive heart failure (See **Cardiovascular** below).
- AVANDIA may be associated with an increased risk of cardiac ischemia. **AVANDIA is not recommended in patients with a history of ischemic heart disease, particularly those with myocardial ischemic symptoms** (See **Cardiovascular** below).
- AVANDIA 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

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

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

The use of AVANDIA 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**
AVANDIA can cause fluid retention, congestive heart failure, and may be associated with an increased risk of ischemia. Some studies have reported an increased cardiovascular risk with AVANDIA compared to another member of the thiazolidinedione class, pioglitazone. **AVANDIA 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:** AVANDIA 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. Thiazolidinediones, like AVANDIA, 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, including excessive, rapid weight gain; dyspnea; and/or edema. 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).

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

Treatment with thiazolidinediones has been associated with cases of congestive heart failure, some of which were difficult to treat unless the medication was discontinued. AVANDIA should be discontinued if any deterioration in cardiac status occurs.
An increase in reporting of fluid retention related events including congestive heart failure has been seen in patients receiving AVANDIA in combination with metformin and a sulfonylurea. This triple therapy regimen is not an approved indication and is not recommended.

In trials in which AVANDIA was added to insulin, AVANDIA increased the risk of congestive heart failure. Coadministration of AVANDIA and insulin is not recommended.

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 AVANDIA 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 AVANDIA is therefore not recommended for patients being treated with nitrates.**

Cardiovascular Events in a Group of 52 Clinical Trials: In a meta-analysis 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 meta-analysis of 46 placebo-controlled trials (rosiglitazone N=8,124, placebo N=5,636) ranging in duration from 8 to 104 weeks a statistically significant increased risk of myocardial infarction (0.4% versus 0.2%, OR 2.23 [95% CI: 1.14, 4.64]) and congestive heart failure (0.9% versus 0.6%, OR 2.20 [95% CI: 1.40, 3.51]) and a statistically non- significant increased risk of MACE (0.7% versus 0.5%, OR 1.53 [95% CI: 0.94, 2.54]) were observed with AVANDIA versus placebo.

Cardiovascular Events in a Prospectively Designed Cardiovascular Outcomes Clinical Trial: In RECORD, a prospectively designed, open-label, randomised cardiovascular outcomes study (4,447 patients), a difference in risk of the primary endpoint of cardiovascular death or cardiovascular hospitalization was not observed for AVANDIA compared with active control. However, in a subgroup of AVANDIA users with a history of ischemic heart disease (383 out of 2220 patients) there was a non-significant increase in cardiovascular death or cardiovascular hospitalization (Hazard Ratio 1.26; 95% CI [0.95, 1.68]) (see ADVERSE REACTIONS, Adverse Drug Reaction Overview).

**AVANDIA is not recommended in patients with a history of ischemic heart disease, particularly those with myocardial ischemic symptoms.**

**Edema:** AVANDIA should be used with caution in patients with edema. In healthy volunteers who received AVANDIA 8 mg once daily as monotherapy for 8 weeks, there was a statistically significant increase in median plasma volume (1.8 mL/kg) compared with 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 AVANDIA 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 AVANDIA and temporarily administer insulin. AVANDIA may be reinstituted after the acute episode is resolved.

**Hypoglycemia:** Because AVANDIA does not stimulate insulin secretion, hypoglycemia is not expected to occur when AVANDIA is prescribed as monotherapy. Patients receiving AVANDIA 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 AVANDIA 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).

**Hematologic**

In controlled trials, there were dose related decreases in hemoglobin and hematocrit. The magnitude of the decreases ($\leq$ 11 g/L for hemoglobin and $\leq$ 0.034 for hematocrit) was small for AVANDIA alone and AVANDIA 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 AVANDIA dose and remained relatively constant thereafter. Decreases may be related to increased plasma volume observed during treatment with AVANDIA 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 AVANDIA 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 post-marketing experience with AVANDIA, 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 AVANDIA in all patients and periodically thereafter per the clinical judgement of the healthcare professional.

Patients with mildly elevated liver enzymes (ALT levels ≤ 2.5 times the upper limit of normal) at baseline or during therapy with AVANDIA should be evaluated to determine the cause of the liver enzyme elevation.

Initiation of, or continuation of, therapy with AVANDIA in patients with mild liver enzyme elevations (ALT levels ≤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 AVANDIA, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain > 3 times the upper limit of normal, therapy with AVANDIA 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 AVANDIA should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

**Musculoskeletal**

In post-marketing experience, there have been very rare cases of creatinine kinase (CK) elevation, myalgia, and rhabdomyolysis reported with the use of rosiglitazone.

**Fractures:** Long-term studies (ADOPT and RECORD) showed an increased incidence of bone fractures in patients taking AVANDIA. 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 AVANDIA.

Decreases in spine and hip bone mineral density have been reported in men and women taking rosiglitazone in epidemiological and randomized clinical trials.

**Ophthalmologic**

New onset and/or worsening macular edema with decreased visual acuity has been reported rarely in post-marketing experience with AVANDIA. In some cases, the visual events resolved or improved following discontinuation of AVANDIA. 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, AVANDIA 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 events 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 AVANDIA in pregnant women. Rosiglitazone has been reported to cross the human placenta and to be detectable in fetal tissues. AVANDIA 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, AVANDIA 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 AVANDIA is excreted in human milk. Because many drugs are excreted in human milk, AVANDIA should not be administered to a nursing woman.

**Pediatrics (< 18 years of age)**: There are no data on the use of AVANDIA in patients under 18 years of age; therefore, AVANDIA 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 hemoglobin A1C measurements should be performed to monitor therapeutic response.

Liver enzyme monitoring is recommended prior to initiation of therapy with AVANDIA 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 AVANDIA.

In clinical trials, edema was reported in 4.8% of patients taking AVANDIA 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 events 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 AVANDIA 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 AVANDIA was added to a sulfonylurea (see WARNINGS AND PRECAUTIONS, Cardiovascular).

In double blind studies where AVANDIA was administered for up to one year, serious adverse experiences of ischemic heart disease were reported in 1.3% of patients taking AVANDIA 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 AVANDIA 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).

Cardiovascular Events in a Group of 52 Clinical Trials: In a meta-analysis 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.

Cardiovascular Events in a Prospectively designed cardiovascular outcomes Clinical Trial: In a prospectively designed cardiovascular outcomes study, RECORD, (mean follow-up 5.5 years; 4,447 patients) (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions) there was no difference in the risk of the primary endpoint of cardiovascular death or cardiovascular hospitalization for AVANDIA on background sulfonylurea or metformin monotherapy versus sulfonylurea plus metformin.

In a subgroup of rosiglitazone users with a history of Ischemic Heart Disease of a large cardiovascular outcomes trial (RECORD) (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], p=0.055) (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 AVANDIA 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 AVANDIA, 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 AVANDIA occurred consistently over the duration of the study (see CLINICAL TRIALS).

Long-term studies showed an increased incidence of bone fracture in patients taking AVANDIA (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 AVANDIA 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 events rarely led to withdrawal. Reports of anemia were greater in patients treated with a combination of AVANDIA and metformin (7.1%) compared to monotherapy with AVANDIA or AVANDIA 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 events reported in clinical trials of rosiglitazone (8 weeks to 1 year) as monotherapy are shown in Table 1.

**Table 1 Adverse Events (≥ 5% in Any Treatment Group) Reported by Patients in Double-blind Clinical Trials with AVANDIA as Monotherapy (8 weeks to 1 year)**

| | AVANDIA N = 2526 | | Placebo N = 601 | | Metformin N = 225 | | Sulfonylureas* N = 626 | |
|---|---|---|---|---|---|---|---|---|
| **Preferred Term** | **N** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| **Total Pts. w/adverse events** | 1742 | **69.0** | 374 | **62.2** | 172 | **76.0** | 438 | **70.0** |
| Upper respiratory tract infection | 251 | **9.9** | 52 | **8.7** | 20 | **8.9** | 46 | **7.3** |
| 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 patients receiving glyburide (N=514), gliclazide (N=91) or glipizide (N=21)
** includes cuts, burns, sprains, fractures, falls, accidents and surgical procedures.

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

**Long-term Trials of AVANDIA as Monotherapy:** In a 4 to 6 year monotherapy study (ADOPT), adverse reactions observed with AVANDIA 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 AVANDIA (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 AVANDIA were reported in the upper arm, hand and foot (see WARNINGS AND PRECAUTIONS, Fractures).

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

The mean age of patients in this trial was 58 years, 52% were male, and the mean duration of follow-up was 5.5 years. AVANDIA demonstrated non-inferiority to active control for the primary endpoint of cardiovascular hospitalization or cardiovascular death (HR 0.99, 95% CI: 0.85-1.16, non-inferiority p = 0.02). There were no significant differences between groups for secondary endpoints with the exception of congestive heart failure (see Table 2). The incidence of congestive heart failure was significantly greater among patients randomized to AVANDIA.

**Table 2 Cardiovascular (CV) Outcomes for RECORD Trial**

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

There was an increased incidence of bone fractures for subjects randomized to AVANDIA in addition to metformin or sulfonylurea compared to those randomized to metformin plus sulfonylurea (8.3% versus 5.3%; RR 1.57, 95% CI 1.26, 1.97; p<0.001) (see WARNINGS AND PRECAUTIONS, Fractures). The majority of fractures were reported in the upper limbs and distal lower limbs. The risk of fracture was higher in females relative to control (11.5% versus 6.3%; RR 1.82, 95% CI 1.37, 2.41; p<0.001), than in males relative to control (5.3% versus 4.3%; RR 1.23, 95% CI 0.85, 1.77; p=0.3160). Additional data are necessary to determine whether there is an increased risk of fracture in males after a longer period of follow-up.

**Echocardiographic Study**

AVANDIA is contraindicated in patients with heart failure. Patients with congestive heart failure (CHF) New York Heart Association (NYHA) Class I and II treated with AVANDIA 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 AVANDIA treatment

compared with placebo during the 52-week study (see Table 3).

**Table 3 Emergent Cardiovascular Adverse Events in Patients with Congestive Heart Failure (NYHA Class I and II) treated with AVANDIA or Placebo (in addition to Background Antidiabetic and CHF Therapy)**

| Events | Placebo<br>N = 114<br>n (%) | AVANDIA<br>N = 110<br>n (%) |
|---|---|---|
| **Adjudicated** | | |
| Cardiovascular Deaths | 4 (4) | 5 (5) |
| CHF Worsening | 4 (4) | 7 (6) |
| With overnight hospitalization | 4 (4) | 5 (5) |
| Without overnight hospitalization | 0 (0) | 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 | 5 (4) | 10 (9) |
| Myocardial Infarction | 2 (2) | 5 (5) |
| Angina | 3 (3) | 6 (5) |

*Includes hospitalization for any cardiovascular reason

## Abnormal Hematologic and Clinical Chemistry Findings

**Hematological:** Small decreases in hematological parameters were more common in the patients treated with AVANDIA than in placebo-treated patients. Leukopenia was reported in 0.4% of AVANDIA 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 AVANDIA. 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 AVANDIA (see Table 5, ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

**Serum Transaminase Levels:** In clinical studies in 4598 patients treated with AVANDIA (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 AVANDIA had reversible elevations in ALT > 3 times the upper limit of the reference range compared with 0.2% on placebo, 0.9% on metformin and 0.3% on sulfonylureas.

Hyperbilirubinemia was found in 0.3% of patients treated with AVANDIA 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 AVANDIA (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 AVANDIA, 0.59 for placebo-treated patients, and 0.78 for patients treated with active comparator agents. In the RECORD cardiovascular outcomes trial, patients randomized to AVANDIA in addition to metformin or sulfonylurea (10,849 patient-years exposure) and to metformin plus sulfonylurea (10,209 patient years exposure) had a rate of ALT increase to ≥3X upper limit of normal of approximately 0.2 and 0.3 per 100 patient-years exposure, respectively.

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

**Post-Market Adverse Drug Reactions**

In post-marketing experience with AVANDIA 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 AVANDIA have been received rarely. These patients frequently reported concurrent peripheral edema. In some cases, symptoms improved following discontinuation of AVANDIA (see WARNINGS AND PRECAUTIONS, Ophthalmologic).

Reports of anaphylactic reaction (such as angioedema and urticaria), rash and pruritus, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been received very rarely.

In post-marketing experience, there have been very rare cases of creatinine kinase (CK) elevation, myalgia, and rhabdomyolysis reported with the use of rosiglitazone.

Long-term post-market studies have shown an increased incidence of bone fracture in patients taking AVANDIA (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.

Post-marketing reports of parotid gland enlargement have been associated with rosiglitazone and approximately one third of the reports resolved or improved following discontinuation of AVANDIA.

## DRUG INTERACTIONS

### Overview

**Drugs Metabolized by Cytochrome $P_{450}$:** It has been shown *in vitro* that AVANDIA 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:** AVANDIA (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 AVANDIA 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 AVANDIA.

## Drug-Drug Interactions

**Oral Contraceptives:** In 32 healthy women, AVANDIA (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 AVANDIA 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:** AVANDIA (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 AVANDIA. No clinically significant reductions in glimepiride AUC and $C_{max}$ were observed after repeat doses of AVANDIA for 8 days in healthy adult subjects.

**Metformin:** Concurrent administration of AVANDIA (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 AVANDIA.

**Digoxin:** Repeat oral dosing of AVANDIA (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 AVANDIA (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 AVANDIA 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 AVANDIA.

**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 a maximum of 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 AVANDIA used in combination with a sulfonylurea should not exceed 4 mg daily (see Recommended Dose and Dosage Adjustment, Combination Therapy with sulfonylurea).

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

AVANDIA 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 AVANDIA 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). AVANDIA 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 AVANDIA 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 AVANDIA in combination with metformin is 4 mg administered as either a single dose once daily or in divided doses twice daily. The dose of AVANDIA 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 AVANDIA 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 AVANDIA 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 AVANDIA 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 AVANDIA 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, AVANDIA 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.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

AVANDIA 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. AVANDIA 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 AVANDIA 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 AVANDIA 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.

AVANDIA 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 AVANDIA 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 AVANDIA 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 AVANDIA 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 AVANDIA is 8 mg. Phase II studies indicated that no additional benefit was obtained with a total daily dose of 12 mg.

AVANDIA 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 AVANDIA 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 AVANDIA 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 AVANDIA (see Table 4). In addition, AVANDIA 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 4 Weight Changes (kg) from Baseline During Clinical Trials with AVANDIA**

| Treatment Group | Duration | Control Group | Control Group | AVANDIA 4 mg | AVANDIA 8 mg |
|---|---|---|---|---|---|
| | | | median ($25^{th}$, $75^{th}$ percentile) (range) | median ($25^{th}$, $75^{th}$ percentile) (range) | median ($25^{th}$, $75^{th}$ percentile) (range) |
| **Monotherapy** | | | | | |
| AVANDIA | 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 |
| AVANDIA | 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 |
| AVANDIA | 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** | | | | | |
| AVANDIA + 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 | - |
| AVANDIA + 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 AVANDIA. In all 26-week controlled trials, across the recommended dose range, AVANDIA 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 5).

Increases in LDL occurred primarily during the first 1 to 2 months of therapy with AVANDIA 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 AVANDIA 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 AVANDIA in combination with sulfonylurea or metformin were generally similar to those seen with AVANDIA in monotherapy.

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

**Table 5 Summary of Lipid Changes in 26-Week Placebo-Controlled and 26-Week/52-Week Glyburide-Controlled Monotherapy Studies**

| Parameter | Placebo-controlled Studies Week 26 | | | Glyburide-controlled Study Week 26 and Week 52 | | | |
|---|---|---|---|---|---|---|---|
| | Placebo | AVANDIA | | Glyburide titration | | AVANDIA 8 mg | |
| | | 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 AVANDIA does not stimulate insulin secretion, hypoglycemia is not expected to occur when AVANDIA is prescribed as monotherapy. Patients receiving AVANDIA 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, AVANDIA 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 6). The elimination half-life is 3 to 4 hours and is independent of dose.

**Table 6 Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral Doses (n=32)**

| Parameter | 1 mg Fasting | 2 mg Fasting | 8 mg Fasting | 8 mg Fed |
|---|---|---|---|---|
| $AUC_{0\text{-inf}}$ [ng.h/mL] | 358 (112) | 733 (184) | 2971 (730) | 2890 (795) |
| $C_{max}$ [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

**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 AVANDIA 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, AVANDIA 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, AVANDIA 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 AVANDIA 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 with healthy subjects. As a result, unbound $C_{max}$ and $AUC_{0\text{-}inf}$ were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects. Therapy with AVANDIA 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 with 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 AVANDIA is contraindicated in these patients.

## STORAGE AND STABILITY

Store at controlled room temperature 15º C to 30º C.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

AVANDIA tablets contain rosiglitazone maleate equivalent to 2, 4 or 8 mg rosiglitazone.

Each pentagonal film-coated TILTAB tablet contains rosiglitazone as the maleate as follows: 2 mg-pink, debossed with SB or GSK on one side and “2” on the other; 4 mg-orange, debossed with SB or GSK on one side and “4” on the other; 8 mg-red-brown, debossed with SB or GSK on one side and “8” on the other.

**Non-medicinal Ingredients:** hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, and triacetin and one or more of the following: synthetic red and yellow iron oxides, and talc.

**Presentations:** 2 mg bottles of 60’s, 4 mg bottles of 100’s and 8 mg bottles of 60’s.

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

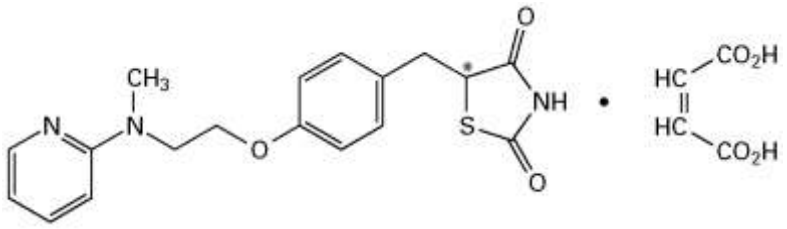
Proper name: Rosiglitazone maleate

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: 473.52 (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

### Monotherapy

A total of 2315 patients with type 2 diabetes, previously treated with diet alone or antidiabetic medication(s), were treated with AVANDIA 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 AVANDIA produced statistically significant improvements in FPG and A1C compared to baseline and relative to placebo (Table 7).

**Table 7 Glycemic Parameters in Two 26-Week Placebo-Controlled Trials**

| **Study A** | **Placebo** | **AVANDIA 2 mg twice daily** | **AVANDIA 4 mg 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)** | | | |
| Baseline (mean) | 0.09 | 0.09 | 0.088 |
| Change from baseline (mean) | 0.009 | -0.003 | -0.006 |
| Difference from placebo (adjusted mean) | | -0.012* | -0.015* |
| **Responders (≥ 0.007 decrease in ratio from baseline)** | 6% | 40% | 42% |

| **Study B** | **Placebo** | **AVANDIA 4 mg once daily** | **AVANDIA 2 mg twice daily** | **AVANDIA 8 mg once daily** | **AVANDIA 4 mg 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, AVANDIA 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 8.

**Table 8 A1C (ratio) by Prior Therapy in Two 26-Week Placebo Controlled Trials (Pooled Data)**

| | **Placebo** | **AVANDIA 4 mg once daily** | **AVANDIA 2 mg twice daily** | **AVANDIA 8 mg once daily** | **AVANDIA 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 AVANDIA 4 mg once daily or 8 mg once daily. Statistically significant improvements in A1C compared to baseline were observed for AVANDIA 4 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 AVANDIA 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 AVANDIA compared to 4 mg of AVANDIA.

**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 AVANDIA 2 mg twice daily (N=195) or AVANDIA 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 AVANDIA 4 mg twice daily; -1.41 mmol/L and -0.0027 with AVANDIA 2 mg twice daily; and -1.67 mmol/L and -0.0072 with glyburide. For A1C, the difference between AVANDIA 4 mg twice daily and glyburide was not statistically significant at week 52. The initial fall in FPG with glyburide was greater than with AVANDIA; however, this effect was less durable over time. The improvement in glycemic control seen with AVANDIA 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**

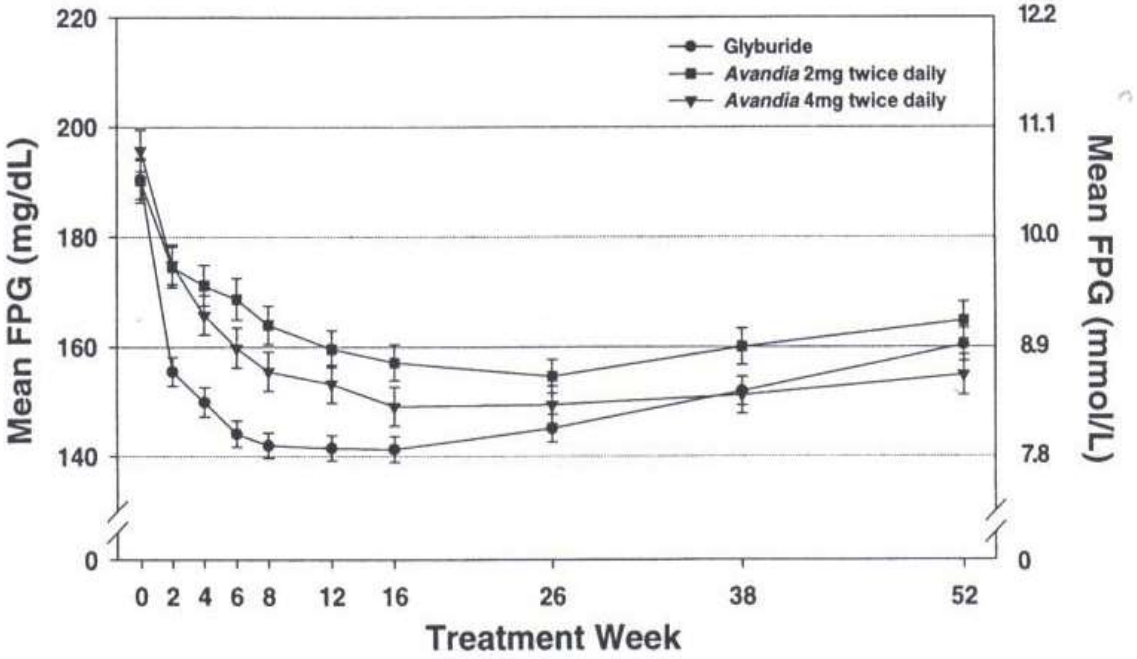
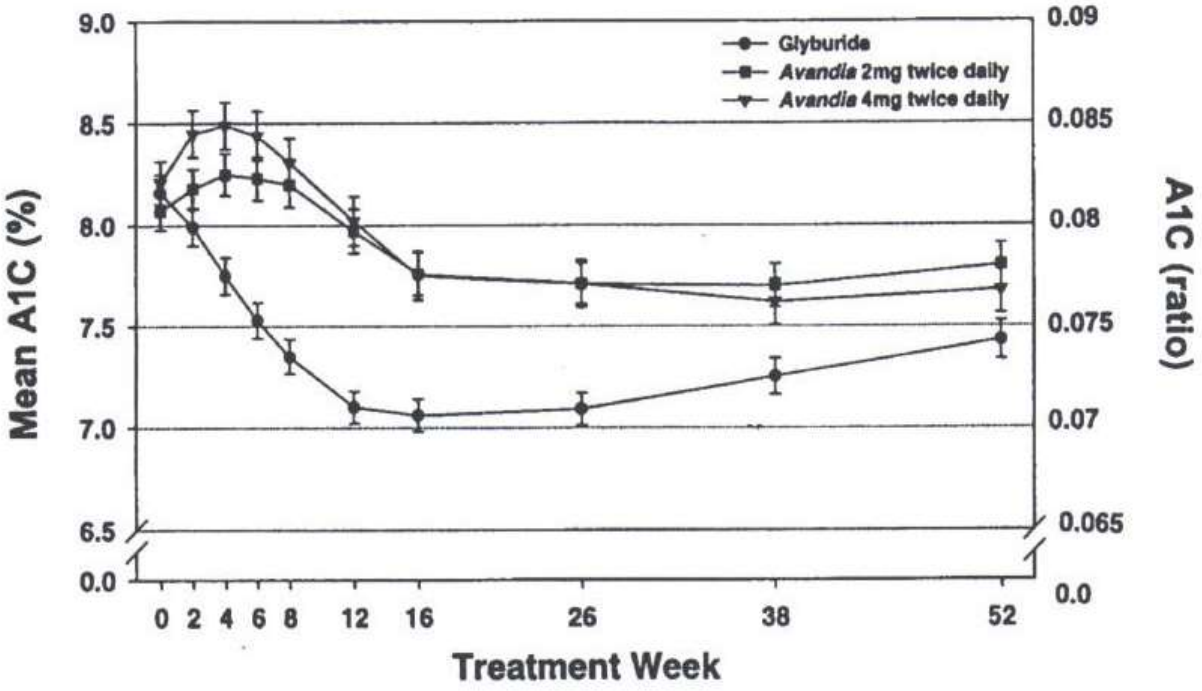



**Figure 2: Mean A1C Over Time in a 52-Week Glyburide-Controlled Study**



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 AVANDIA. 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 AVANDIA, respectively versus 1.9 kg in glyburide-treated patients. In patients treated with AVANDIA, 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 AVANDIA 4 mg twice daily (n=104) with glyburide (n=99), treatment with AVANDIA 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 AVANDIA, 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 AVANDIA 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 AVANDIA 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**

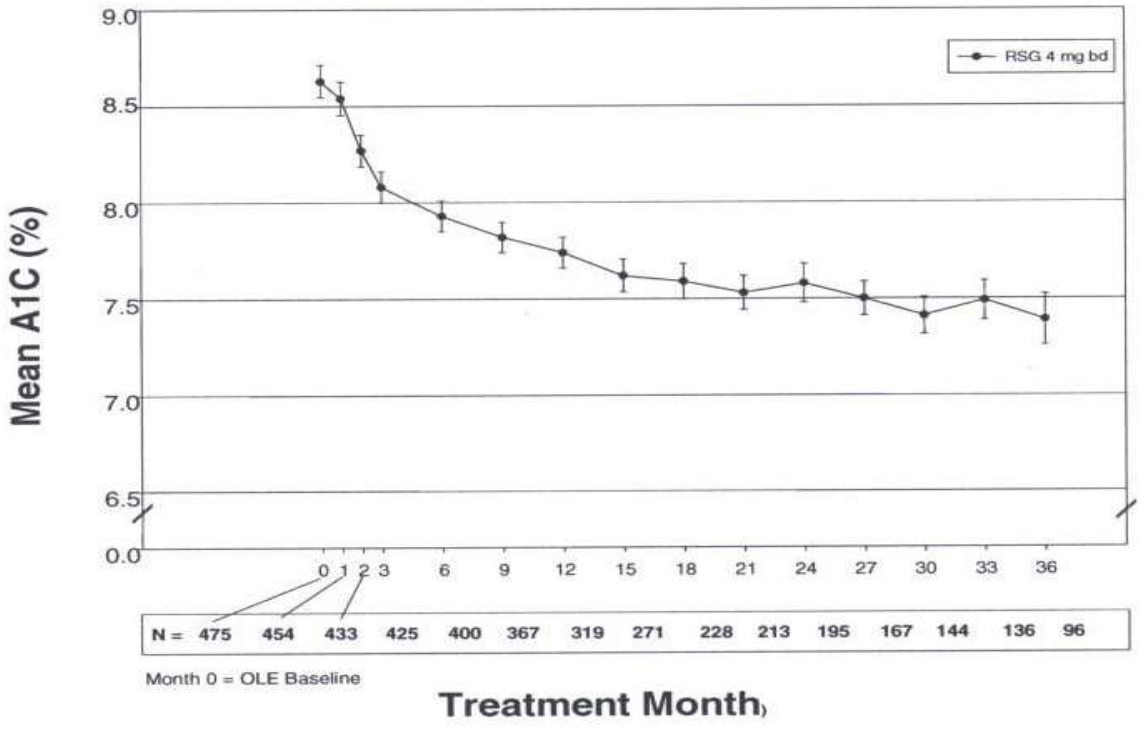



**Figure 4: Mean A1C Over Time**

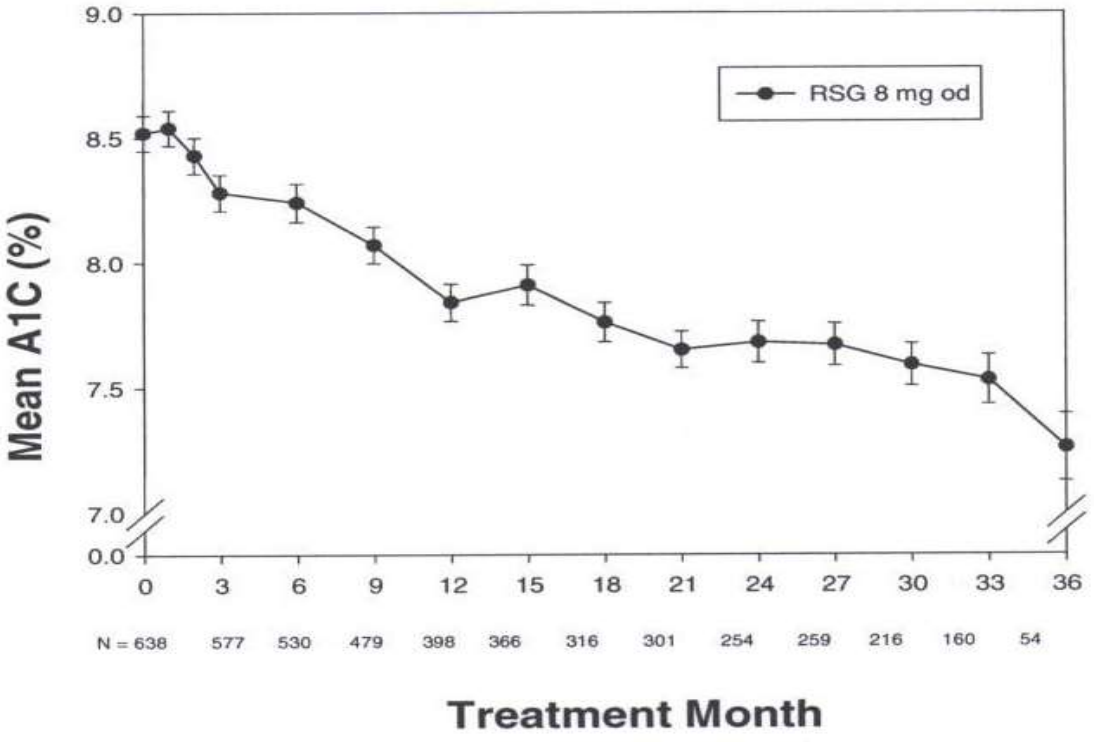


**Figure 5: Mean FPG Over Time**

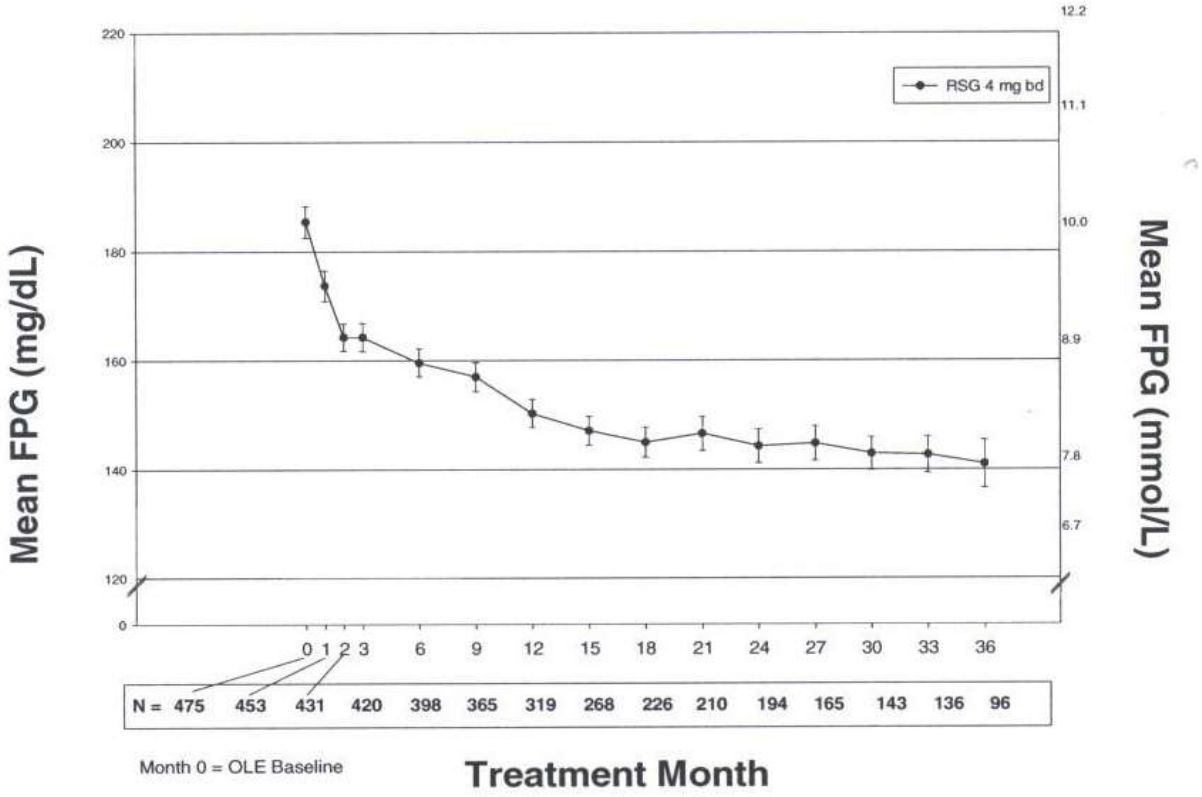
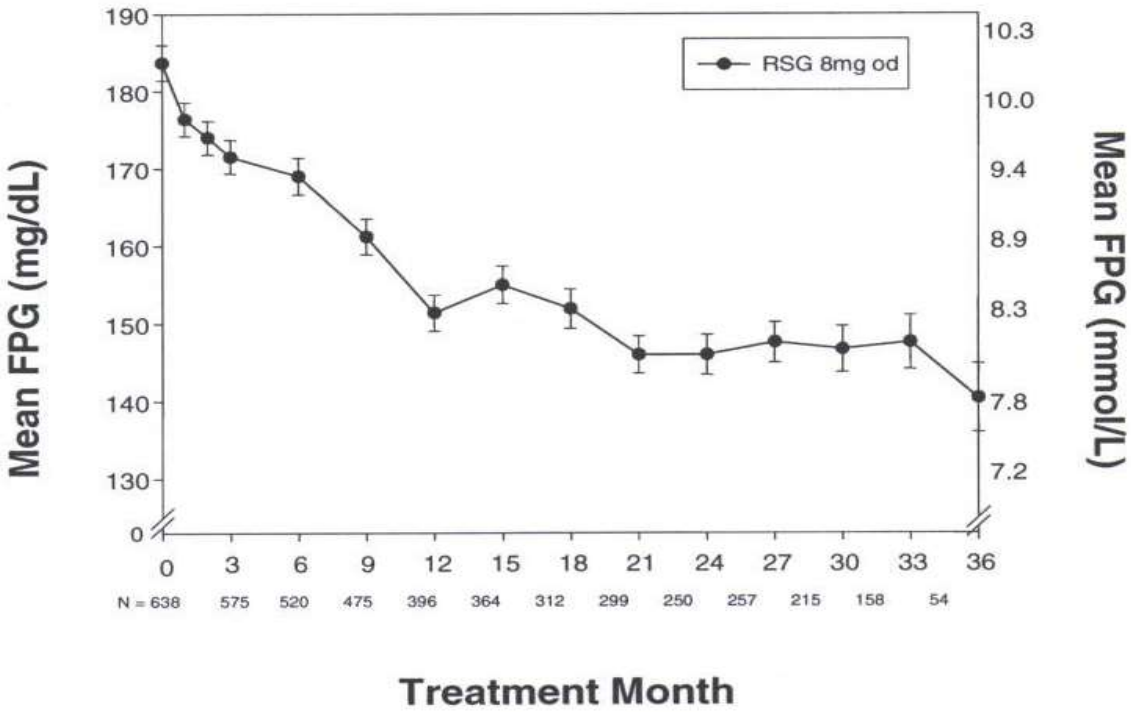



**Figure 6: Mean FPG Over Time**



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 AVANDIA, 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 AVANDIA 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 AVANDIA, 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 AVANDIA, 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 AVANDIA, 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 AVANDIA compared to glyburide or metformin (see WARNINGS AND PRECAUTIONS, Fractures and Adverse Drug Reaction Overview). Otherwise, adverse reactions observed with AVANDIA were generally consistent to those observed in shorter-term trials. AVANDIA 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 AVANDIA arm. The myocardial ischemic event rate observed was similar among patients on AVANDIA, metformin and glyburide.

**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 AVANDIA in combination with metformin. AVANDIA, 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 AVANDIA 4 mg once daily, AVANDIA 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 AVANDIA 4 mg once daily and AVANDIA 8 mg once daily, versus patients continued on metformin alone (Table 9).

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

| | Metformin | AVANDIA 4 mg once daily + metformin | AVANDIA 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% |
| **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 AVANDIA 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 AVANDIA 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 AVANDIA 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 AVANDIA 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**

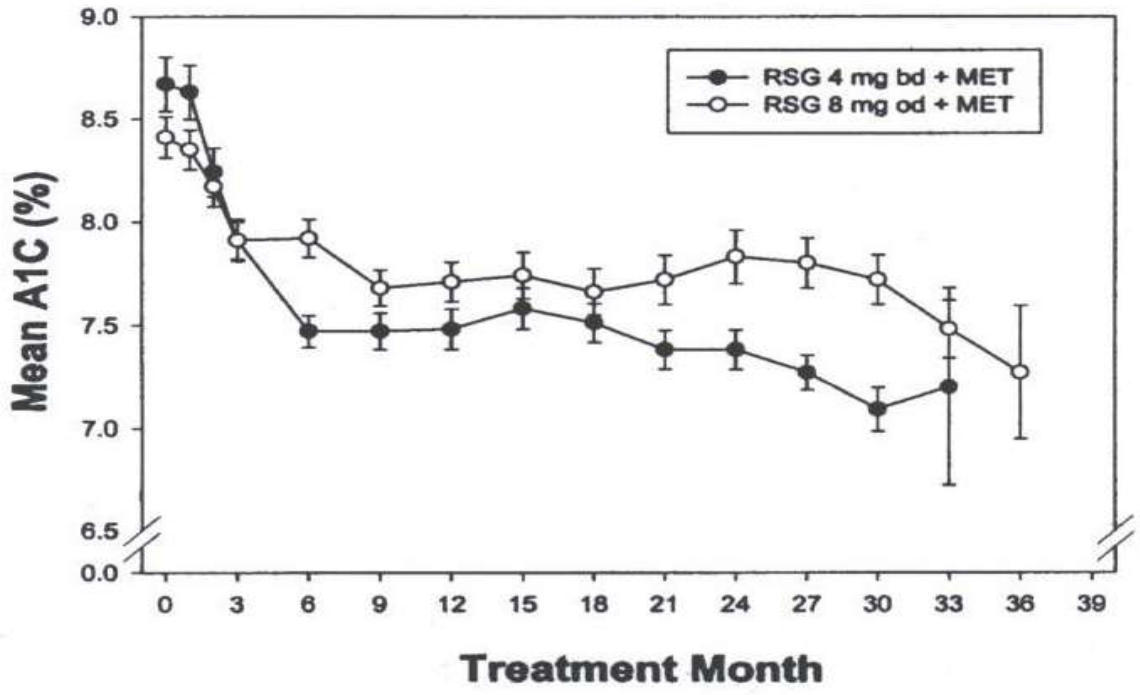
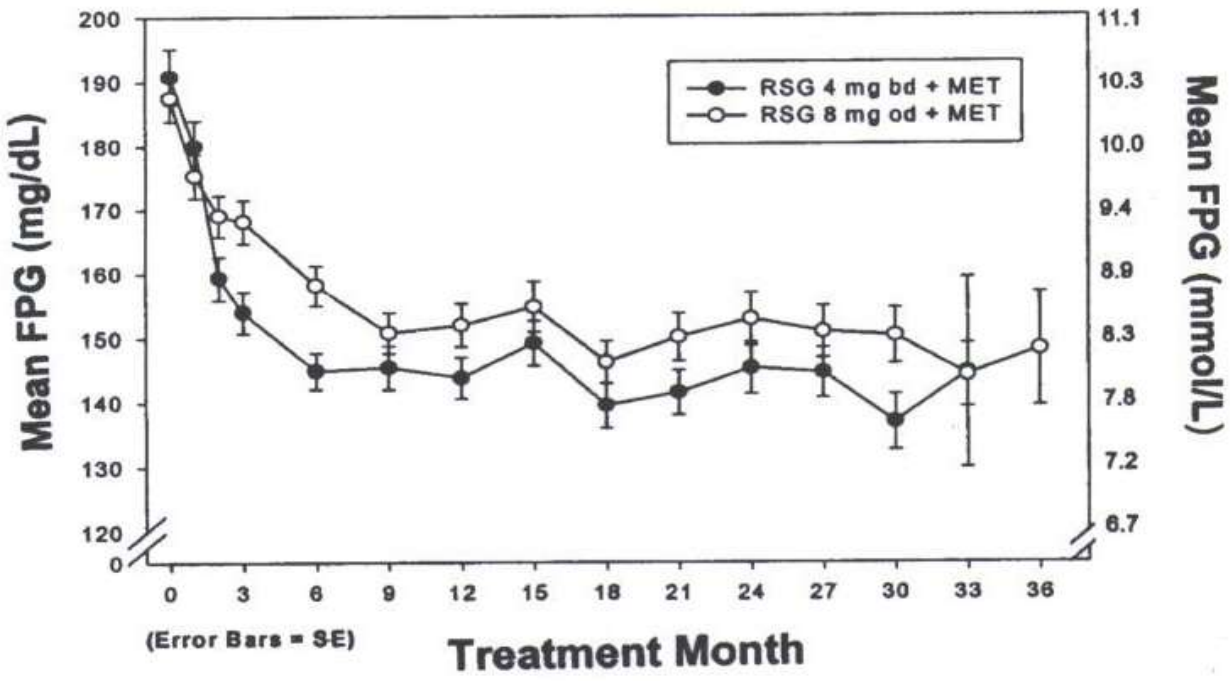


**Figure 8: Mean FPG Values Over Time**




**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 AVANDIA in combination with sulfonylurea. AVANDIA 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 AVANDIA 4 mg daily plus sulfonylurea (n = 397), was assessed in patients inadequately controlled on a sulfonylurea alone. Single or divided doses of AVANDIA 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 10).

**Table 10 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**

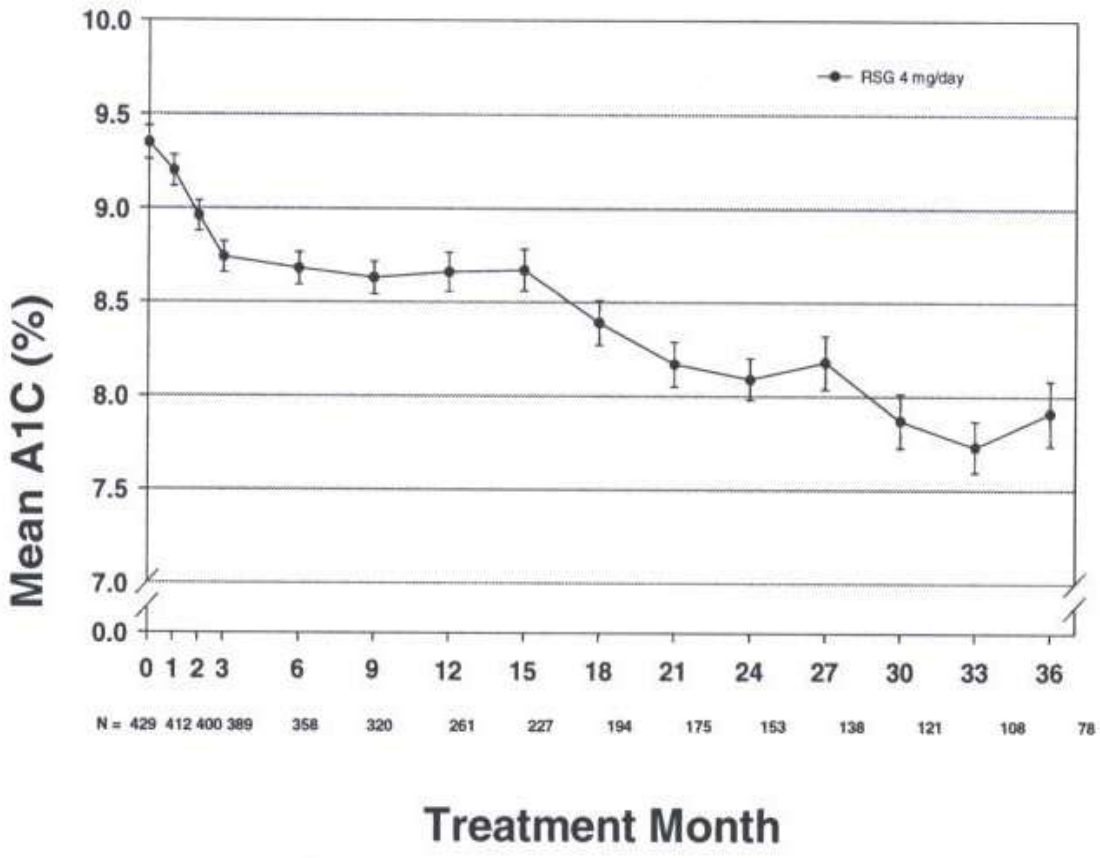
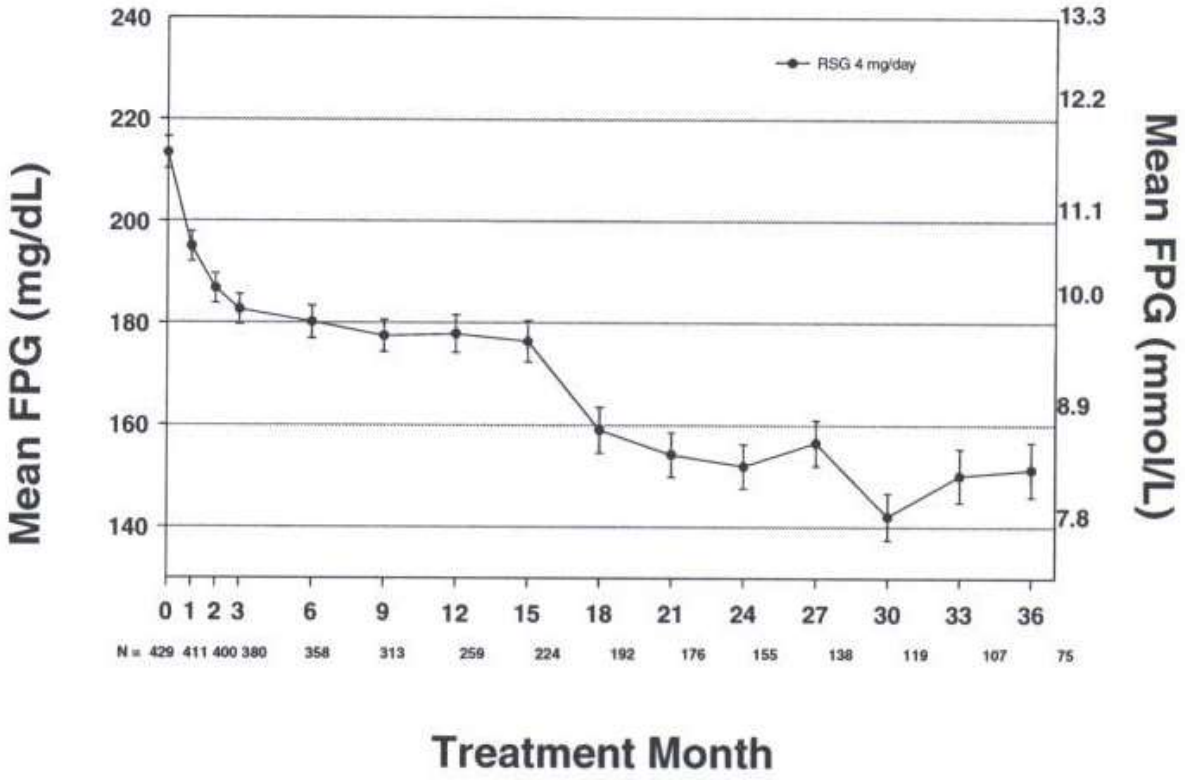


**Figure 10 Mean FPG Over Time**




**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, AVANDIA 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 AVANDIA 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 AVANDIA. 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 AVANDIA plus insulin combination trials (insulin, 5.4%; and AVANDIA 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 AVANDIA (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 AVANDIA 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

**[Pr]AVANDIA**
**rosiglitazone (as rosiglitazone maleate) tablets**

This leaflet is part III of a three-part "Product Monograph" for AVANDIA and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AVANDIA. 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:**
AVANDIA is used with diet and exercise to lower blood sugar:
- In adults with type 2 diabetes.
- When all other diabetes medicines have not lowered blood sugar enough or cannot be used.

AVANDIA may be used alone or with either metformin OR a sulfonylurea to treat your diabetes. However, AVANDIA is not recommended for use with both metformin AND a sulfonylurea together.

Talk about the benefits and side effects with your doctor. Together decide if it is right for you. The doctor will ask you to read and sign a form showing you understand the risks of AVANDIA.

**What it does:**
AVANDIA helps to control high blood sugar. It can help your body respond better to insulin made in your body. AVANDIA does not cause your body to make more insulin.

**When it should not be used:**
- If you have or have had heart problems or heart failure. AVANDIA may increase the risk of serious heart problems.
- If you are allergic to AVANDIA or any of the nonmedicinal ingredients.
- If you have serious liver problems.
- If you are pregnant.

**What the medicinal ingredient is:**
rosiglitazone maleate

**What the nonmedicinal ingredients are:**
hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, and triacetin and one or more of the following: synthetic red and yellow iron oxides, and talc.

**What dosage forms it comes in:**
Tablets: 2 mg, 4 mg and 8 mg.

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**
AVANDIA 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)

AVANDIA should not be used if you have or have had heart problems.

**Before you use AVANDIA, talk to your doctor about other options to treat your diabetes.**

Before you use AVANDIA talk to your doctor or pharmacist about all your medical conditions, including if:
- you have or have had swelling in the wrists, hands, feet or ankles (edema).
- you have been diagnosed with angina (chest pain) 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 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 (polycystic ovary syndrome). AVANDIA could make you ovulate again. This means you could get pregnant. Talk to your doctor about your birth control choices.

AVANDIA can cause a decrease in the amount of calcium and other minerals in your bones. The strength of your bones may be decreased especially in the hips and spine.

AVANDIA is not recommended for use in children under 18 years of age.

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

AVANDIA is not recommended for use with insulin.

AVANDIA is not recommended for use with both metformin **and** a sulfonylurea together.

## INTERACTIONS WITH THIS MEDICATION

AVANDIA may affect how other medicines work and some medicines may affect how AVANDIA works.

Tell your doctor about all medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

In particular, tell your doctor if you are using any of the following medicines:

- drugs used to lower cholesterol and triglyceride levels in your blood (gemfibrozil)
- drugs used to treat tuberculosis (rifampin)
- drugs used to treat psoriasis or rheumatoid arthritis (methotrexate).
- drugs for heart pain (nitrate medicines). Examples are nitroglycerine or isosorbide dinitrate.

## PROPER USE OF THIS MEDICATION

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

Take AVANDIA:

- by mouth.
- with or without food.
- each day. Either once a day (in the morning) or twice a day (in the morning and in the evening).

Diet and exercise can help your body control its blood sugar better. It is important to stay on the diet and exercise program recommended by your doctor.

**Usual Starting dose:** 4 mg per day.

Your doctor will decide on the dose of AVANDIA that is best for you.

**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 AVANDIA **once a day** and miss one dose, take the dose as soon as you remember.

If you take AVANDIA **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 AVANDIA, just take your dose as usual the next day. Don't try to make it up by taking extra tablets.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

**If any of the side effects listed becomes severe or troublesome, tell your doctor or pharmacist.**

Side effects may include:

Common side effects:

- Broken bones, usually in the hand, upper arm or foot. Talk to your doctor about the risk of fracture.
- A small increase in total cholesterol levels.
- Weight gain in a short period of time.

Uncommon side effects:

- Constipation.
- Increased hunger.

Very rare side effects:

- Abnormal vaginal bleeding or spotting.
- Swelling of the parotid gland (salivary glands located over the jaw, in front of the ears).

AVANDIA can cause abnormal liver and blood sugar test results. Your doctor will decide when to perform blood tests and will interpret the results.

Your doctor should check your eyes regularly. Some patients may experience vision changes. This can be due to swelling in the back of the eye while taking AVANDIA.

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| **Symptom / effect** | | **Talk with your doctor** | | **Stop taking AVANDIA and call your doctor immediately** |
| | | **Only if severe** | **In all cases** | |
| **Common** | **Anemia** (Low red blood cell count): Feeling very weak or tired. | | ✓ | |
| | **Edema (**Fluid retention): swelling in arms and legs, hands and feet. Rapid or unexpected increase in weight. | | ✓ | |
| | **Hypoglycemia** (Low blood sugar levels): Dizziness, lack of energy, drowsiness, headache, trembling sweating, or hunger. | ✓ | | |
| | **Heart failure or fluid in the lungs** (pulmonary edema): Trouble breathing or shortness of breath, getting tired easily after light physical activity such as walking, unusual tiredness, severe breathlessness which worsens on lying down, waking up short of breath at night, an unusually rapid increase in weight,swollen ankles or feet. | | | ✓ |
| | **Angina:** Chest pain | | ✓ | |
| **Rare** | **Liver problems**: Nausea, vomiting, stomach pain, lack of appetite, tiredness, dark urine, or yellowing of the skin or eyes. | | | ✓ |
| | Blurred vision or decreased vision | | | ✓ |
| **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). | | | ✓ |

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| **Symptom / effect** | | **Talk with your doctor** | | **Stop taking AVANDIA and call your doctor immediately** |
| | | **Only if severe** | **In all cases** | |
| | **Muscle Disorders:** Muscle tenderness or weakness, muscle pain that you cannot explain. | | ✓ | |
| | **Fatigue:** Generalized weakness, especially if you do not feel well. | | ✓ | |
| | **Hematuria:** Brownish or discoloured urine. | | | ✓ |

This is not a complete list of side effects. If you experience any unexpected effects while taking AVANDIA**,** contact your doctor or pharmacist.

## HOW TO STORE IT

Store AVANDIA at room temperature (15°C to 30°C). Keep out of reach and sight of children.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting ( https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. 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 at:
http://www.gsk.ca
or by contacting the sponsor,
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7333 Mississauga Road
Mississauga, Ontario
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