PRODUCT MONOGRAPH

Pr AVANDARYL®

rosiglitazone maleate and glimepiride

4 mg/1 mg Tablets
4 mg rosiglitazone (as rosiglitazone maleate) and 1 mg glimepiride

4 mg/2 mg Tablets
4 mg rosiglitazone (as rosiglitazone maleate) and 2 mg glimepiride

4 mg/4 mg Tablets
4 mg rosiglitazone (as rosiglitazone maleate) and 4 mg glimepiride

Antidiabetic Agent

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Date of Revision:
March 1, 2011

Submission Control No: 143643

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[Pr]AVANDARYL®

rosiglitazone maleate and glimepiride

PART I: HEALTH PROFESSIONAL INFORMATION

Note: for additional information on rosiglitazone maleate and glimepiride, consult the individual Product Monographs.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet/ 4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg	lactose monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

AVANDARYL® (rosiglitazone maleate and glimepiride) is indicated for use 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 AVANDARYL®, physicians must:

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

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 AVANDARYL®, 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 suggests that use in the geriatric population is associated with differences in safety and effectiveness (see WARNINGS AND PRECAUTIONS, Cardiovascular, WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, and WARNINGS AND PRECAUTIONS, Special Populations).

Pediatrics (< 18 years of age):
There are no data on the use of AVANDARYL® in patients younger than 18 years. Furthermore, thiazoledinediones promote the maturation of preadipocytes and have been associated with weight gain. Therefore, AVANDARYL® is not indicated in patients younger than 18 years of age.

CONTRAINDICATIONS

AVANDARYL® is contraindicated in:

- Patients with New York Heart Association (NYHA) Class I to IV heart failure.
- Type 1 diabetes (formerly known as insulin-dependent diabetes mellitus or IDDM)
- Patients with known hypersensitivity to rosiglitazone maleate, glimepiride, other sulfonylureas or sulphonamides, or any of the ingredients of AVANDARYL®.
- Patients with serious hepatic impairment (see WARNINGS AND PRECAUTIONS).
- Patients with Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
- Pregnancy or breastfeeding women. 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

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

AVANDARYL®

Administration with other drugs: For safety reasons, the use of AVANDARYL® in combination with insulin is not indicated (see CLINICAL TRIALS).

The use of AVANDARYL® in combination with metformin (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 dose adjustment of the rosiglitazone maleate or glimepiride components may be needed when AVANDARYL® is co-administered with CYP2C8 or CYP2C9 inhibitors or inducers (see DRUG INTERACTIONS).

Rosiglitazone maleate

Due to its mechanism of action, rosiglitazone is active only in the presence of endogenous insulin. Therefore, AVANDARYL® should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Carcinogenesis and Mutagenesis

See TOXICOLOGY.

Cardiovascular

Rosiglitazone maleate

Rosiglitazone can cause fluid retention, congestive heart failure, and may be associated with an increased risk of cardiac ischemia. Some studies have reported an increased cardiovascular risk with rosiglitazone compared to another member of the thiazolidinedione class, pioglitazone. **AVANDARYL® should be used only when all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance.**

Congestive heart failure: Thiazolidinediones, like rosiglitazone maleate, alone or in combination with other antidiabetic agents, can cause fluid retention, which can exacerbate or lead to congestive heart failure. The fluid retention may very rarely present as rapid and excessive weight gain. All patients should be monitored for signs and symptoms of adverse reactions relating to fluid retention and heart failure. In particular, patients who are at risk for heart failure including those receiving concurrent therapy which increases insulin levels (i.e. sulfonylureas) should be closely monitored (see ADVERSE REACTIONS). An increase in reporting of fluid retention related events including congestive heart failure has been seen in patients receiving rosiglitazone in combination with metformin and a sulfonylurea. This triple therapy regimen is not an approved indication.

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

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

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

Ischemic heart disease: In a retrospective analysis of data from pooled clinical studies (n=14,237), which included patients on combination therapy with insulin as well as patients with NYHA Class I and II heart failure, the overall incidence of events typically associated with cardiac ischemia was higher for rosiglitazone 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 AVANDARYL® is therefore not recommended for patients being treated with nitrates.**

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

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

Edema: AVANDARYL® should be used with caution in patients with edema. The maximum approved dose of rosiglitazone to be used in combination with a sulfonylurea is 4 mg. In healthy volunteers who received rosiglitazone maleate 8 mg once daily as monotherapy for 8 weeks, there was a statistically significant increase in median plasma volume (1.8 mL/kg) compared to placebo. In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was observed at a greater frequency in patients treated with rosiglitazone maleate and may be dose related (see ADVERSE REACTIONS). For information on macular edema, see WARNINGS AND PRECAUTIONS, Ophthalmologic.

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

Glimepiride

It has been suggested, based on a study conducted by the University Group Diabetes Program (UGDP), that certain sulfonylurea antidiabetic agents increase cardiovascular mortality in diabetic patients, a population at greater risk of cardiovascular disease. This finding was not confirmed by a more recent trial, the United Kingdom Prospective Diabetes Study (UKPDS) which showed that intensive glycemic control with either sulfonylureas or insulin did not have an adverse effect on cardiovascular outcomes. Despite questions regarding the design of these studies and interpretation of the results, the results of these studies provide a basis for caution, especially high risk patients with cardiovascular disease.

In clinical trials more patients receiving glimepiride and insulin reported an increase in peripheral edema compared to patients receiving insulin alone.

Endocrine and Metabolism

Hypoglycemia: AVANDARYL® is a combination tablet containing rosiglitazone maleate and glimepiride, a sulfonylurea. All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Elderly, debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of glimepiride. A starting dose of 1 mg glimepiride, as contained in AVANDARYL® 4 mg/1 mg, followed by appropriate dose titration is also recommended in these patients (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).

Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when other drugs with blood-glucose lowering potential are used.

Patients receiving rosiglitazone maleate in combination with a sulfonylurea may be at risk for hypoglycemia, and a reduction in the dose of either agent may be necessary (see DOSAGE AND ADMINISTRATION, Specific Patient Populations).

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 AVANDARYL® and temporarily administer insulin. AVANDARYL® may be reinstituted after the acute episode is resolved.

If risk factors for hypoglycemia are present, including renal insufficiency, low body weight, malnourishment or co-administration of certain other drugs (see WARNINGS AND PRECAUTIONS, Hypoglycemia, DRUG INTERACTIONS, and DOSAGE AND ADMINISTRATION), it may be necessary to adjust the dosage of glimepiride or the entire therapy during such situations. This also applies whenever illness occurs during therapy or the patient's life-style changes.

Rosiglitazone maleate

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

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

Hematologic

Rosiglitazone maleate

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

Glimepiride

Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD)-deficiency with sulfonylurea agents can lead to hemolytic anemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

Hepatic

Rosiglitazone maleate

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

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

In postmarketing experience with rosiglitazone, 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 AVANDARYL® 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 AVANDARYL® should be evaluated to determine the cause of the liver enzyme elevation.

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

Ophthalmologic

Rosiglitazone maleate

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

Renal

Rosiglitazone maleate

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 DOSING AND ADMINISTRATION, Dosing Considerations, and ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency).

Glimepiride

In patients with renal insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions (see DOSAGE AND ADMINISTRATION).

There are no data from the use of glimepiride in patients on renal dialysis (see ACTION AND CLINICAL PHARMACOLOGY).

Sexual Function/Reproduction

Rosiglitazone maleate

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

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

Special Populations

Pregnant Women: There are no controlled trials of AVANDARYL® in pregnant women. Rosiglitazone has been reported to cross the human placenta and to be detectable in fetal tissues. AVANDARYL® 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.

Teratogenic Effects: In animal studies rosiglitazone maleate was not teratogenic but treatment during mid-late gestation caused fetal death and growth retardation in both rats and rabbits at 19- and 73-fold clinical systemic exposure, respectively. In animal studies, glimepiride did not produce teratogenic effects but has been shown to be associated with intrauterine fetal death in rats when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses inducing maternal hypoglycaemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride (see TOXICOLOGY, Teratogenic Effects).

Nonteratogenic Effects: In some studies in rats, offspring of dams exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformations consisting of shortening, thickening and bending of the humerus during the postnatal period. Significant concentrations of glimepiride were observed in the serum and breast milk of the dams as well as in the serum of the pups. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride.

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug. at the time of delivery. Patients who are planning a pregnancy should consult their physician.

Labour and Delivery: The effect of AVANDARYL® or its components on labour and delivery in humans is not known.

Nursing Women: No studies have been conducted with AVANDARYL®. Rosiglitazone and/or its metabolites have been detected in the milk of lactating rats. In rat reproduction studies, significant concentrations of glimepiride were observed in the serum and breast milk of the dame, as well as in the serum of the pups. Although it is not known whether rosiglitazone and/or glimepiride are excreted in human milk, many drugs, including other sulfonylureas, are excreted in human milk. Since the potential for hypoglycemia in nursing infants exist, and because of the effects on nursing animals (see above Pregnant Women, Nonteratogenic Effects), AVANDARYL® should not be administered to a nursing woman. If AVANDARYL® is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered (see Pregnant Women).

Pediatrics (< 18 years of age): There are no data on the use of AVANDARYL® in patients under 18 years of age. Furthermore thiazoledinediones promote the maturation of preadipocytes and have been associated with weight gain. Therefore AVANDARYL® is not indicated for use in patients under 18 years of age.

Geriatrics (≥ 65 years of age):

Rosiglitazone maleate

Evidence from clinical studies and experience suggest that use in the geriatric population may be associated with differences in safety (see WARNINGS & PRECAUTIONS, Cardiovascular).

Glimepiride

Glimepiride is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Elderly patients are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Therefore, the initial dosing, dose increments, and maintenance dosage should be conservative based upon blood glucose levels prior to and after initiation of treatment to avoid hypoglycemic reactions (see WARNINGS AND PRECAUTIONS, Hypoglycemia and DOSING AND ADMINISTRATION, Specific Patient Populations).

Monitoring and Laboratory Tests

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

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In clinical trials, reports of hypoglycemia in patients treated with rosiglitazone maleate and sulfonylurea combination therapy were similar to reports in patients treated with sulfonylurea monotherapies. In double-blind studies, hypoglycemia was reported by 5.2% of patients receiving rosiglitazone maleate in combination with a sulfonylurea, by 5.9% receiving sulfonylurea monotherapy, by 0.6% receiving rosiglitazone maleate monotherapy, and by 0.2% receiving placebo.

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

The overall incidence of hypoglycemia with glimepiride in placebo controlled trials was approximately 14%. In two long-term (2-2.5 years) and well-controlled studies, the incidence of hypoglycemic reaction ranged from 2.1 to 3.1%.

Rosiglitazone maleate

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

In clinical trials, edema was reported in 4.8% of patients taking rosiglitazone maleate as monotherapy compared to 1.3% on placebo, 1.0% on sulfonylureas and 4.0% on rosiglitazone maleate in combination with sulfonylureas. Treatment was required for 1.2% of patients on rosiglitazone maleate monotherapy with an adverse event of edema. In these clinical trials, few patients (1.0%) were enrolled with a presenting medical condition of congestive heart failure (NYHA Class I/II). Edema was more frequently observed when rosiglitazone maleate was used in combination with a sulfonylurea (see WARNINGS AND PRECAUTIONS, General, and Cardiovascular and CLINICAL TRIALS).

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

In double blind studies where rosiglitazone maleate was administered for up to one year, serious adverse experiences of ischemic heart disease were reported in 1.3% of patients taking rosiglitazone maleate compared to 0.5% on placebo, 0.8% on sulfonylureas and 1.2% on rosiglitazone maleate in combination with sulfonylureas.

In clinical trials, dose-related weight gain was seen with rosiglitazone maleate alone and in combination with other hypoglycemic agents (see ACTION AND CLINICAL PHARMACOLOGY and WARNINGS AND PRECAUTIONS).

In a retrospective analysis of data from pooled clinical studies, which included patients on combination therapy with insulin as well as patients with NYHA Class I and II heart failure, the overall incidence of events typically associated with cardiac ischemia was higher for rosiglitazone 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, Rosiglitazone maleate, Ischemic heart disease).

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

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

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

Anemia was reported in 1.9% of patients taking rosiglitazone maleate as monotherapy compared to 0.7% on placebo, 0.6% on sulfonylureas and 2.0% on rosiglitazone maleate in combination with a sulfonylurea.

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

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

Glimepiride

Adverse events, other than hypoglycemia, considered to be possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with glimepiride included dizziness (1.7%), asthenia (1.6%), headache (1.5%), and nausea (1.1%).

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*.

Rosiglitazone maleate

Controlled Clinical Trials: The incidence and types of adverse events reported in controlled, 26-week clinical trials in association with rosiglitazone maleate in combination with a sulfonylurea, in comparison to adverse events reported in association with rosiglitazone maleate and sulfonylurea monotherapies are shown in Table 1.

Table 1 Adverse Events (≥ 5% in Any Treatment Group) Reported by Patients in 26-week Double-blind Clinical Trials with Rosiglitazone Maleate as Monotherapy or in Combination with a Sulfonylurea

	Rosiglitazone Maleate N=2526	**Placebo** N=601	**Sulfonylurea** N=626	**Rosiglitazone Maleate 4 mg plus sulfonylurea** N=405
Preferred term	%	%	%	%
Upper respiratory tract infection	9.9	8.7	7.3	8.6
Injury*	7.6	4.3	6.1	6.7
Headache	5.9	5.0	5.4	4.9
Back pain	4.0	3.8	5.0	2.0
Hyperglycemia	3.9	5.7	8.1	4.2
Fatigue	3.6	5.0	1.9	1.7
Hypoglycemia	0.6	0.2	5.9	5.2
Dizziness	2.5	1.7	3.0	5.4
Hypercholesterolemia	3.4	0.5	1.3	5.2

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

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

Long-term Trials of Rosiglitazone: In a 4 to 6 year monotherapy study, fractures were reported in a greater number of females with rosiglitazone (9.3%, 2.7/100 patient-years) compared to glyburide (3.5%, 1.3/100 patient-years) or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the females who received rosiglitazone were reported in the upper arm, hand and foot (see WARNINGS AND PRECAUTIONS, Fractures and Adverse Drug Reaction Overview).

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

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

Bone fracture (female and male); n (%) subjects [no. of events]	RSG (N=2220)	MET/SU (N=2227)	Relative risk (95% CI)	p-value
Any event	185 (8.3) [225]	118 (5.3) [132]	1.57 (1.26, 1.97)	p <0.001
Upper limb	86 (3.9) [101]	55 (2.5) [58]	1.57 (1.12, 2.19)	p=0.0095
Distal lower limb	70 (3.2) [101]	27 (1.2) [28]	2.60 (1.67, 4.04)	p<0.001
Femur/hip	10 (0.5) [11]	8 (0.4) [8]	1.25 (0.50, 3.17)	
Spine	14 (0.6) [14]	9 (0.4) [9]	1.56 (0.68, 3.60)	
Pelvis	0	4 (0.2) [4]	NA	
Other	25 (1.1) [26]	25 (1.1) [25]	1.00 (0.58, 1.74)	
Bone fracture in female subjects, n (%) subjects [no. of events]	RSG (N=1078)	MET/SU (N=1075)	Relative risk (95% CI)	p-value
Any event	124 (11.5) [154]	68 (6.3) [78]	1.82 (1.37, 2.41)	p<0.001
Upper limb	63 (5.8) [78]	36 (3.3) [39]	1.75 (1.17, 2.61)	p=0.0075
Distal lower limb	47 (4.4) [49]	16 (1.5) [17]	2.93 (1.67, 5.13)	p<0.001
Femur/hip	7 (0.6) [8]	7 (0.7) [7]	1.00 (0.35, 2.83)	
Spine	8 (0.7) [8]	4 (0.4) [4]	1.99 (0.60, 6.60)	
Pelvis	0	1 (<0.1) [1]	NA	
Other	11 (1.0) [11]	10 (0.9) [10]	1.10 (0.46, 1.94)	
Bone fracture in male subjects, n (%) subjects [no. of events]	RSG (N=1142)	MET/SU (N=1152)	Relative risk (95% CI)	p-value
Any event	61 (5.3) [71]	50 (4.3) [54]	1.23 (0.85, 1.77)	p=0.3160
Upper limb	23 (2.0) [23]	19 (1.6) [19]	1.22 (0.67, 2.23)	p=0.6261
Distal lower limb	23 (2.0) [24]	11 (1.0) [11]	2.11 (1.03, 4.31)	p=0.0521
Femur/hip	3 (0.3) [3]	1 (<0.1) [1]	3.03 (0.32, 29.05)	
Spine	6 (0.5) [6]	5 (0.4) [5]	1.21 (0.37, 3.96)	
Pelvis	0	3 (0.3) [3]	NA	
Other	14 (1.2) [15]	15 (1.3) [15]	0.94 (0.46, 1.94)	

Glimepiride

Digestive Tract Reactions: Gastrointestinal (GI) disturbances e.g. nausea, GI fullness, occur occasionally. Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was similar to that of placebo. In rare cases, there may be elevation of liver enzyme levels. Sulfonylureas, including glimepiride, may also, in isolated instances, cause impairment of liver function (e.g. with cholestasis and jaundice), as well as hepatitis which may also lead to liver failure.

Dermatologic Reactions: Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of glimepiride. If those hypersensitivity reactions persist or worsen, the drug should be discontinued. Porphyria cutanea tarda, photosensitivity reactions, and allergic vasculitis, in some cases, progressing from mild to serious reactions (including anaphylactic shock) have been reported with sulfonylureas, including glimepiride.

Hematologic Reactions: Leukopenia, agranulocytosis, hemolytic anemia, thrombocytopenia, aplastic anemia, erythrocytopenia, granulocytopenia, and pancytopenia have been reported with sulfonylureas, including glimepiride.

Metabolic Reactions: Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas; however, no cases have yet been reported with glimepiride. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. Although there have been no reports for glimepiride, the syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Other Adverse Reactions: Changes in accommodation and/or blurred vision may occur with the use of glimepiride. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment. In placebo-controlled trials of glimepiride, the incidence of blurred vision was placebo, 3.4%, and glimepiride, 1.7%.

Human Ophthalmology Data: Ophthalmic examinations were carried out in over 500 subjects during long-term studies of glimepiride using the methodology of Taylor and West and Laties et al. No significant differences were seen between glimepiride and glyburide in the number of subjects with clinically important changes in visual acuity, intra-ocular tension, or in any of the five lens-related variables examined. Ophthalmic examinations were carried out during long-term studies using the method of Chylack et al. No significant or clinically meaningful differences were seen between glimepiride and glipizide with respect to cataract progression by subjective LOCS II grading and objective image analysis systems, visual acuity, intraocular pressure, and general ophthalmic examination.

Abnormal Hematologic and Clinical Chemistry Findings

Hematological: Small decreases in hematological parameters were more common in the patients treated with rosiglitazone maleate than in placebo-treated patients. Leukopenia was reported in 0.4% of rosiglitazone maleate patients compared to 0.2% of patients on placebo, 0.6% on sulfonylureas and 1.1% on rosiglitazone maleate in combination with sulfonylureas. Decreases may be related to increased plasma volume observed with treatment with rosiglitazone maleate. The mean decrease in hemoglobin was approximately 10 to 12 g/L; the decrease in hematocrit was 0.03 to 0.04.

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

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

In the controlled trials (including patients with ALT/AST of up to 2.5 times the upper limit of the reference range at study entry), 0.2% of patients treated with rosiglitazone maleate had reversible elevations in ALT >3 times the upper limit of the reference range compared to 0.2% on placebo and 0.5% on active comparators. Hyperbilirubinemia was found in 0.3% of patients treated with rosiglitazone maleate compared with 0.9% treated with placebo and 1% in patients treated with active comparators. Overall, there was a decrease in mean values for ALT, AST, alkaline phosphatase and bilirubin over time in patients treated with rosiglitazone maleate (see WARNINGS AND PRECAUTIONS, Hepatic).

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

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

Post-Market Adverse Drug Reactions

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

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

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

Reports of anaphylactic reaction, rash and pruritus have been received very rarely.

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

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

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

DRUG INTERACTIONS

Overview

Rosiglitazone maleate

Drugs Metabolized by Cytochrome P_{450}: It has been shown *in vitro* that rosiglitazone 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 CYP 2C8 and may inhibit the metabolism of drugs primarily metabolized by CYP 2C8 (e.g. paclitaxel, rosiglitazone, repaglinide). No *in vivo* interaction studies have been performed with the 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 maleate 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 maleate may be needed when CYP2C8 inhibitors are co-administered.

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

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

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

Glimepiride

Glimepiride is metabolized by CYP2C9. This should be taken into account when glimepiride is co-administered with inducers or inhibitors of CYP2C9.

Co-administration of glimepiride with CYP2C9 inhibitors (e.g. fluconazole) resulted in increased glimepiride plasma concentrations. Since there is a potential for an increase in the risk of dose-related adverse reactions (e.g. hypoglycemia), a decrease in glimepiride dose may be needed when CYP2C9 inhibitors are co-administered.

Drug-Drug Interactions

AVANDARYL®

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

Rosiglitazone maleate

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

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

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

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

Methotrexate: An interaction study of 22 adult patients with psoriasis examined the effect of repeat doses of rosiglitazone maleate (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 maleate 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 maleate.

Glimepiride

Coadministration of acetylsalicylic acid (1 g three times daily) and glimepiride led to a 34% decrease in the mean glimepiride AUC and, therefore, a 34% increase in the mean CL/f. The mean C_{max} had a decrease of 4%. Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported.

Coadministration of either cimetidine (800 mg once daily) or ranitidine (150 mg twice daily) with a single 4-mg oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride, and no differences were seen in hypoglycemic symptomatology.

Concomitant administration of propranolol (40 mg three times daily) and glimepiride significantly increased C_{max}, AUC, and $T_{1/2}$ of glimepiride by 23%, 22%, and 15%, respectively, and it decreased CL/f by 18%. The recovery of the major metabolites, cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2), from urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo. Pooled data from clinical trials in patients with type 2 diabetes showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of beta-blockers. However, if beta-blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

Concomitant administration of glimepiride tablets (4 mg once daily) did not alter the pharmacokinetic characteristics of R- and S- warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding. Glimepiride treatment did result in a slight, but statistically significant, decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride treatment were very small (3.3% and 9.9%, respectively) and are unlikely to be clinically important.

The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2 mg glimepiride were unaffected by coadministration of ramipril (an ACE inhibitor) 5 mg once daily in normal subjects. No hypoglycemic symptoms were reported.
A study conducted in twelve normal healthy volunteers showed that fluconazole (an inhibitor of CYP2C9) administered as 200 mg once daily, increased glimepiride systemic exposure approximately two and a half-fold (see WARNINGS AND PRECAUTIONS, General).

A study conducted in ten normal healthy volunteers showed that rifampin (an inducer of CYP2C9) administered as 600 mg once daily, decreased glimepiride systemic exposure by 34% (see WARNINGS AND PRECAUTIONS, General).

Potential interactions of glimepiride with other drugs metabolized by cytochrome P_{450} 2C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid. Although no specific interaction studies were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of calcium-channel blockers, estrogens, fibrates, NSAIDS, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone.

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including anabolic steroids and male sex hormones, ACE inhibitors, insulin and other oral antidiabetics nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as azapropazone, sulfonamides (e.g. sulphaphenazole), chloramphenicol, clarithromycin, coumarins, cyclophosphamine, disopyramide, fenyramidol, fenfluramine, fibrates, fluconazole, fluoxetine, guanethidine, ifosfamide, miconazole, monoamine oxidase inhibitors, oxyphenbutazone, para-aminosalicylic acid, pentoxifylline (high dose parenteral), phenylbutazone, probenecid, propranolol, quinolones, salicylates, sulfonamide antibiotics, sulfinpyrazone and tetracyclines. When these drugs are administered to a patient receiving glimepiride, the patient should be observed closely for hypoglycemia. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, acetazolamide, barbiturates, corticosteroids, diazoxide, epinephrine and other sympathomimetic agents, glucagon, isoniazid, laxatives (after protracted use), nicotinic acid (in high dose), estrogens and progestogens, phenothiazines, phenytoin, rifampin and thyroid products. When these drugs are administered to a patient receiving glimepiride, the patient should be closely observed for loss of glycemic control. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for hypoglycemia.

H_2 receptor antagonists, beta-blockers, clonidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect.

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
AVANDARYL® should be given once daily with a meal. The dosage of antidiabetic therapy with AVANDARYL® should be individualized on the basis of effectiveness and tolerability. No exact dosage relationship exists between AVANDARYL® and other antidiabetic agents.

No studies have been performed specifically examining the safety and efficacy of AVANDARYL® in patients previously treated with other oral hypoglycemic agents and switched to AVANDARYL®. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

Specific Patient Populations
AVANDARYL® should not be used in pregnancy or in nursing mothers. There are no data on the use of AVANDARYL® in patients younger than 18 years; therefore, the use of AVANDARYL® in pediatric patients is not recommended.

In elderly, debilitated, or malnourished patients, or in patients with renal insufficiency, the initial dosing, dose increments, and maintenance dosage of AVANDARYL® should be conservative to avoid hypoglycemic reactions (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, and WARNINGS AND PRECAUTIONS, Hypoglycemia). 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 AVANDARYL® 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) (see WARNINGS AND PRECAUTIONS, Hepatic and ACTION AND CLINICAL PHARMACOLOGY, Hepatic Insufficiency). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with AVANDARYL® and periodically thereafter. AVANDARYL® is contraindicated in patients with serious hepatic impairment (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Hepatic).

Recommended Dose and Dosage Adjustment

AVANDARYL® is available for oral administration as tablets containing a fixed dose of 4 mg rosiglitazone maleate with variable doses of glimepiride (1, 2, or 4 mg) in a single tablet formulation.

For patients inadequately controlled on rosiglitazone or sulfonylurea monotherapy, the usual starting dose of AVANDARYL® is 4 mg/1 mg or 4 mg/2 mg once daily. When switching from combination therapy of rosiglitazone maleate plus glimepiride as separate tablets, the usual starting dose of AVANDARYL® is the dose of rosiglitazone maleate and glimepiride already being taken. The maximum recommended daily dose of AVANDARYL® is 4 mg of rosiglitazone maleate and 4 mg of glimepiride.

Sufficient time should be given to assess adequacy of therapeutic response. Fasting glucose should be used to determine the therapeutic response to AVANDARYL®.

- For patients previously treated with rosiglitazone monotherapy switched to AVANDARYL®, dose titration is recommended if patients are not adequately controlled after 1 to 2 weeks. If additional glycemic control is needed, the daily dose of AVANDARYL® may be increased by increasing the glimepiride component in no more than 2 mg increments at 1 to 2 week intervals up to the maximum recommended total daily dose of 4 mg rosiglitazone maleate/4 mg glimepiride.

- For patients previously treated with sulfonylurea monotherapy switched to AVANDARYL®, it may take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of the rosiglitazone component. If additional glycemic control is needed, the dose of the glimepiride component may be increased. The dose of the rosiglitazone component should not exceed 4 mg. As with other sulfonylurea-containing antidiabetic agents, no transition period is necessary when transferring patients to AVANDARYL®. Patients should be observed carefully (1 to 2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to glimepiride due to potential overlapping of drug effect.

- If hypoglycemia occurs during up-titration of the dose or while maintained on therapy, a dosage reduction of the sulfonylurea component of AVANDARYL® may be considered.

Missed Dose

If a dose of AVANDARYL® is missed, the patient should be advised to take the dosage as soon as they remember anytime during the day. If a whole day is missed, the usual dose should be taken the next day. The patient should be advised not to take a double dose.

OVERDOSAGE

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

No data are available with regard to overdosage of AVANDARYL®. Overdosage of glimepiride can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Rosiglitazone maleate 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. The use of rosiglitazone maleate results in increased responsiveness of insulin-dependent tissues and significantly improves hepatic and peripheral (muscle) tissue sensitivity to insulin in patients with type 2 diabetes. Clinical studies in patients with type 2 diabetes treated with rosiglitazone maleate either as monotherapy or in combination with sulfonylureas showed improved beta-cell function and decreased fasting plasma glucose, insulin and C-peptide values following 26 weeks of treatment. A homeostasis model assessment (HOMA) was conducted using fasting plasma glucose and insulin or C-peptide levels as a measure of insulin sensitivity and beta-cell function. In these studies, reductions in mean plasma pro-insulin and pro-insulin split product concentrations were also observed.

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

Studies between 8 and 26 weeks with rosiglitazone maleate have shown a statistically significant reduction in markers of inflammation, C-reactive protein (CRP) and matrix metalloproteinase-9 (MMP-9). The clinical significance of these effects are still unknown. Further long term clinical trials are needed.

Estimates of LDL particle size can be determined by the LDL cholesterol (LDL) to apolipoprotein B (Apo B) ratio. In controlled clinical trials, rosiglitazone maleate 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 maleate in an open-label study.

The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of glimepiride. This is supported by both preclinical and clinical studies demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These findings are consistent with the results of a long-term, randomized, placebo-controlled trial in which glimepiride therapy improved postprandial insulin/C-peptide responses and overall glycemic control without producing clinically meaningful increases in fasting insulin/C-peptide levels. However, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established.

Pharmacodynamics and Clinical Effects

In clinical studies, treatment with rosiglitazone maleate resulted in an improvement in glycemic control, as measured by fasting plasma glucose (FPG) and hemoglobin A1c (HbA1C), with a concurrent reduction in insulin and C-peptide levels. Post-prandial glucose and insulin levels were also reduced. This is consistent with the mechanism of action of rosiglitazone as an insulin sensitizer. The improvement in glycemic control was durable, with maintenance of effect for at least 52 weeks. In open-labelled extension studies sustained improvements in glycemic control (as measured by A1C levels) were observed in patients receiving rosiglitazone maleate monotherapy for 36 months.

Rosiglitazone is believed to act primarily on muscle and adipose tissue whereas sulfonylureas act primarily by stimulating the release of insulin from functioning pancreatic beta cells. The co-administration of rosiglitazone maleate with sulfonylureas resulted in significantly improved glycemic control compared to either of these agents alone. These results are consistent with a synergistic effect on glycemic control when rosiglitazone maleate is used in combination with sulfonylureas. In patients whose type 2 diabetes was inadequately controlled with sulfonylurea monotherapy, the addition of rosiglitazone maleate led to reductions in A1C levels that were sustained for over 30 months of treatment, in open-labelled studies.

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

Table 3 Weight Changes (kg) from Baseline During Clinical Trials with Rosiglitazone Maleate

Treatment Group	**Duration**	**Control Group**	**Control Group**	**Rosiglitazone maleate 4 mg**	**Rosiglitazone maleate 8 mg**
			median (25^{th}, 75^{th} percentile) (range)	**median (25^{th}, 75^{th} percentile) (range)**	**median (25^{th}, 75^{th} percentile) (range)**
Monotherapy					
Rosiglitazone maleate	26 weeks	placebo	-0.9 (-2.8, 0.9) (-9.6 to 6.8) n = 210	1.0 (-0.9, 3.6) (-11.6 to 12.7) n = 436	3.1 (1.1, 5.8) (-6.8 to 13.9) n = 439
Rosiglitazone maleate	52 weeks	sulfonylurea	2.0 (0, 4.0) (-11.5 to 12.2) n = 173	2.0 (-0.6, 4.0) (-7.0 to 16.0) n = 150	2.6 (0, 5.3) (-11.0 to 22.0) n = 157
Rosiglitazone	48 months	metformin	-2.4 (-5.4, 0.5) (-46.0 to 12.9) n = 1,441	-	3.5 (0.0, 8.1) (-31.0 to 41.3) n = 1,456
		glyburide	2.0 (-1.0, 4.8) (-28.6 to 24.9) n = 1,441		
Combination Therapy					
Rosiglitazone maleate + sulfonylurea	26 weeks	sulfonylurea	0 (-1.3, 1.2) (-6.0 to 14.0) n = 1043	1.8 (0, 3.1) (-5.0 to 11.5) n = 392	-
Rosiglitazone maleate+ metformin	26 weeks	metformin	-1.4 (-3.2, 0.2) (-7.7 to 5.9) n = 175	0.8 (-1.0, 2.6) (-6.8 to 9.8) n = 100	2.1 (0, 4.3) (-5.4 to 13.1) n = 184

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

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

The pattern of LDL and HDL changes following therapy with rosiglitazone maleate in combination with sulfonylureas was generally similar to those seen with rosiglitazone maleate in monotherapy.

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

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

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

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

Pharmacokinetics

Bioavailability

AVANDARYL®

In a bioequivalence study of AVANDARYL® 4 mg/4 mg, the area under the curve (AUC) and maximum concentration (C_{max}) of rosiglitazone following a single dose of the combination tablet were bioequivalent to rosiglitazone maleate 4 mg concomitantly administered with glimepiride 4 mg under fasted conditions. The AUC and C_{max} of glimepiride following a single fasted 4 mg/4 mg dose was bioequivalent to glimepiride concomitantly administered with rosiglitazone maleate 4 mg (see Tables 5 and 6 - Comparative Bioavailability Data). The rate and extent of absorption of both the rosiglitazone component and glimepiride component of AVANDARYL® when taken with food were equivalent to the rate and extent of absorption of rosiglitazone and glimepiride when administered concomitantly as separate tablets with food.
A single dose, randomized 2-way crossover study was conducted in 30 healthy male and female volunteers under fasting conditions with AVANDARYL® [1 x (4 mg rosiglitazone maleate/4 mg glimepiride)] versus concomitant administration of AVANDIA® (1 x 4 mg rosiglitazone maleate) and Amaryl® (1 x 4 mg glimepiride).

Table 5 Table of the Comparative Bioavailability Data Rosiglitazone

[1 x 4 mg administered as 1 x (4 mg rosiglitazone maleate/4 mg glimepiride) and as 1 x 4 mg rosiglitazone maleate administered concomitantly with 1 x 4 mg glimepiride]
From measured data
Geometric Mean
Arithmetic Mean (CV%)

Parameter	Test AVANDARYL®	Reference AVANDIA†	Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	1097 1269 (25.54)	1099 1245 (74.06)	100	96-104
AUC_I (ng.h/mL)	1134 1296 (24.88)	1136 1275 (67.52)	100	96-104
C_{MAX} (ng/mL)	231.4 263.8 (22.23)	226.1 257.0 (75.28)	102	92-114
T_{MAX}* (h)	1.11 (48.71)	1.14 (93.91)		
$T_{½}$* (h)	3.53 (13.66)	3.55 (18.78)		

† AVANDIA® tablets, manufactured in the U.S. by GlaxoSmithKline Inc.
* expressed as arithmetic mean (%CV) only

Table 6 Table of the Comparative Bioavailability Data Glimepiride

[1 x 4 mg administered as 1 x (4 mg rosiglitazone maleate/4 mg glimepiride) and as 1 x 4 mg glimepiride administered concomitantly with 1 x 4 mg rosiglitazone maleate]
From measured data
Geometric Mean
Arithmetic Mean (CV%)

Parameter	Test AVANDARYL®	Reference Amaryl†	Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	930 988 (35.55)	1022 1089 (33.16)	91	87-96
AUC_I (ng.h/mL)	1035 1093 (33.80)	1082 1157 (33.59)	96	91-100
C_{MAX} (ng/mL)	149 160.8 (40.01)	170 184.1(40.46)	88	76-101
T_{MAX}* (h)	3.63 (45.23)	3.54 (61.57)		
$T_{½}$* (h)	7.48 (31.96)	5.10 (42.02)		

† Amaryl ® tablets, manufactured in the U.S. by Aventis Pharamaceuticals
* expressed as arithmetic mean (%CV) only

The AUC and C_{max} of glimepiride increased in a dose-proportional manner following administration of AVANDARYL® 4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg. Administration of AVANDARYL® with food decreased the rate, but not extent, of rosiglitazone absorption and increased both the rate and extent of absorption of glimepiride compared to the fasted state.

Absorption

Rosiglitazone maleate

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. Maximum plasma concentration (C_{max}) and the area under the curve (AUC_{0-inf}) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range.

Glimepiride

After oral administration, glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with type 2 diabetes have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (C_{max}) at 2 to 3 hours.

Distribution

Rosiglitazone maleate

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.

Glimepiride

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

Metabolism

Rosiglitazone maleate

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 CYP 2C9 contributing as only a minor pathway.

Glimepiride

Glimepiride is completely metabolized by oxidative biotransformation after either IV or oral administration. The major metabolites are the cyclohexyl hydroxyl methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P_{450} 2C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1 is clinically meaningful in humans is not clear.

Excretion

Rosiglitazone maleate

Following oral or intravenous administration of [^{14}C]rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and feces, respectively. The plasma half-life of [^{14}C] related material ranged from 103 to 158 hours. The elimination half-life of rosiglitazone is 3 to 4 hours and is independent of dose.

Glimepiride

When ^{14}C-glimepiride was given as a single dose orally, approximately 60% of the total radioactivity was recovered in the urine in 7days and M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.

Special Populations and Conditions

No pharmacokinetic data are available for AVANDARYL® in the following special populations. Information is provided for the individual components of AVANDARYL®.

Pediatrics: No pharmacokinetic data from studies in pediatric subjects are available for either rosiglitazone or glimepiride.

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.

Comparison of glimepiride pharmacokinetics in type 2 diabetic patients ≤ 65 years and those > 65 years was performed in a study using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean AUC at steady state for the older patients was about 13% lower than that for the younger patients; the mean weight adjusted clearance for the older patients was about 11% higher than that for the younger patients. (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

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. Combination therapy with rosiglitazone maleate and sulfonylureas improved glycemic control in both males and females. In rosiglitazone maleate and sulfonylurea combination studies, a greater therapeutic response was observed in females. For a given body mass index (BMI), females tend to have a greater fat mass than males. Since the molecular target of rosiglitazone, PPARγ, is expressed in adipose tissues, this differentiating characteristic may account, at least in part, for the greater response to rosiglitazone maleate in combination with sulfonylureas in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.

There were no differences between males and females in the pharmacokinetics of glimepiride when adjusted for differences in body weight.

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.

No pharmacokinetic studies to assess the effects of race have been performed, but in placebo-controlled studies of glimepiride in patients with type 2 diabetes, the hypoglycemic effect was comparable in whites (n=536), blacks (n=63), and Hispanics (n=63).

Hepatic Insufficiency: Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound C_{max} and $AUC_{0\text{-}inf}$ were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects. Therapy with AVANDARYL® 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). See WARNINGS AND PRECAUTIONS, Hepatic and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency.

No pharmacokinetic studies of glimepiride have been conducted in subjects with hepatic insufficiency.

Renal Insufficiency: There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients, compared to subjects with normal renal function (see WARNINGS AND PRECAUTIONS, Renal, and DOSING AND ADMINISTRATION, Dosing Considerations).

There are no data from the use of glimepiride in patients on renal dialysis (see WARNINGS AND PRECAUTIONS).

A single-dose glimepiride, open-label study was conducted in 15 patients with renal impairment. Glimepiride (3 mg) was administered to 3 groups of patients with different levels of mean creatinine clearance (Clcr): Group I, Clcr=77.7 mL/min (1.30 mL/sec), n=5; Group II, Clcr=27.7 mL/min (0.462 mL/sec), n=3; and Group III, Clcr=9.4 mL/min (0.16 mL/sec), n=7. Glimepiride was found to be well tolerated in all 3 groups. The results showed that M1 and M2 serum levels (mean AUC values) increased 2.2 and 6.1 times from Group I to Group III as renal function decreased. The apparent terminal half life (T½) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased (44.4%, 21.9%, and 9.3% for Groups I to III).

A multiple-dose glimepiride titration study was also conducted in 16 type 2 diabetic patients with renal impairment using doses ranging from 1-8 mg daily for 3 months. The results were consistent with those observed after single doses. All patients with a Clcr less than 22 mL/min (0.37 mL/sec) had adequate control of their glucose levels with a dosage regimen of only 1 mg daily. The results from this study suggested that a starting dose of 1 mg glimepiride , as in AVANDARYL® 4 mg/1 mg, may be given to type 2 diabetic patients with kidney disease, and the dose may be titrated based on fasting blood glucose levels.

STORAGE AND STABILITY

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

Special Instructions
Dispense in a tight, light-resistant container.

DOSAGE FORMS, COMPOSITION AND PACKAGING

AVANDARYL® tablets contain a fixed dose of 4 mg rosiglitazone maleate with variable doses of glimepiride (1, 2, or 4 mg) in a single tablet formulation: 4 mg rosiglitazone maleate with 1 mg glimepiride (4 mg/1 mg), 4 mg rosiglitazone maleate with 2 mg glimepiride (4 mg/2 mg), and 4 mg rosiglitazone maleate with 4 mg glimepiride (4 mg/4 mg).

Each tablet contains rosiglitazone as the maleate and glimepiride as follows:

4 mg/1 mg: yellow, rounded triangular tablet, debossed with gsk on one side and 4/1 on the other;

4 mg/2 mg: orange, rounded triangular tablet, debossed with gsk on one side and 4/2 on the other;

4 mg/4 mg: pink, rounded triangular tablet, debossed with gsk on one side and 4/4 on the other.

Non-medicinal Ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, hypromellose 2910, magnesium stearate, titanium dioxide, macrogol (polyethylene glycol), and one or more of the following: yellow, red, or black iron oxides.

Presentations: 4 mg/1 mg, 4 mg/2 mg and 4 mg/4 mg in bottles of 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

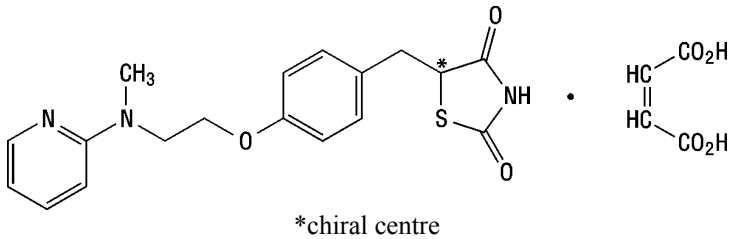
Proper name: Rosiglitazone maleate

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

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

Molecular mass: 473.52 (357.44 free base)

Structural formula:



*chiral centre

Physicochemical properties:

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

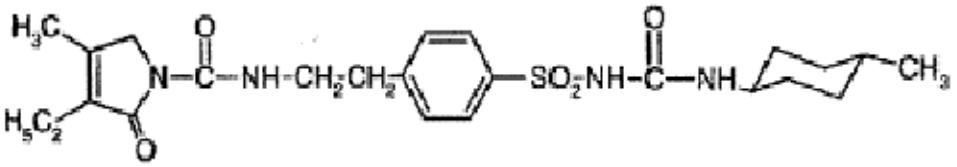
Partition Coefficient: The distribution coefficient of rosiglitazone maleate, was measured by the shake-flask method, using a pH 6.5 phosphate buffer. In n-octanol/water the distribution coefficient was determined to be 194 (logD = +2.29). In cyclohexane/water the distribution coefficient was determined to be 0.32 (logD = - 0.49).

Melting Point: Range of 122°C to 123°C

Drug Substance

Proper name:	Glimepiride
Chemical name:	1-[[p-2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea
Molecular formula:	$C_{24}H_{34}N_4O_5S$
Molecular mass:	490.62

Structural formula:



Physicochemical properties:

Description:	A white to yellowish-white, crystalline, odorless to practically odorless powder
Solubility:	Glimepiride is practically insoluble in water.
pKa:	6.2 ± 0.1 at 37°C
Melting Point:	207°C

CLINICAL TRIALS

The combination of rosiglitazone maleate with a sulfonylurea has been previously approved based on clinical trials in patients with type 2 diabetes inadequately controlled on sulfonylureas alone. The addition of rosiglitazone maleate to a sulfonylurea resulted in significant improvements in glucose concentrations compared to either of these agents alone. These results are consistent with an additive effect on glycemic control when rosiglitazone maleate is used in combination with a sulfonylurea.

Clinical Trials of Rosiglitazone Maleate Add-on Therapy in Patients Not Adequately Controlled on Sulfonylurea Therapy Alone

A total of 1216 patients with type 2 diabetes participated in three 26-week randomized, double-blind, placebo/active-controlled studies designed to assess the efficacy and safety of rosiglitazone maleate in combination with a sulfonylurea. Rosiglitazone maleate administered in either once daily or twice daily dosing regimens was added to the therapy of patients who were inadequately controlled on sulfonylurea alone.

In the first study (Study #1), patients inadequately controlled on a constant dose of sulfonylureas, including glyburide, glipizide or gliclazide (mean baseline FPG 11.4 mmol/L and mean baseline A1C 0.092) were randomized to receive rosiglitazone maleate 1 mg twice daily or rosiglitazone maleate 2 mg twice daily. In the second study (Study #2), patients who were inadequately controlled on at least half-maximal glyburide (≥10 mg/day) were randomized to either rosiglitazone maleate 2 mg once daily or rosiglitazone maleate 4 mg once daily or glyburide alone. In both studies, a statistically significant improvement in FPG (-2.4 to -2.6 mmol/L) and A1C (-0.008 to -0.010) was observed in patients treated with a combination of sulfonylurea and rosiglitazone maleate 4 mg daily versus patients continued on sulfonylurea alone (Table 7).

In the third study, patients with type 2 diabetes inadequately controlled on a maximal dose of glyburide (20 mg daily) who were randomized to receive the combination of rosiglitazone maleate 2 mg twice daily and glyburide (N=98) showed a statistically significant improvement in glycemic control with a mean treatment effect for FPG of -3.1 mmol/L and A1C of -0.014 over glyburide alone. The combination of glyburide and rosiglitazone maleate resulted in lower levels of FPG and A1C than either agent alone. Patients who were inadequately controlled on a maximal dose of glyburide (20 mg daily) and who were switched to the lowest recommended dose of rosiglitazone maleate as monotherapy demonstrated loss of glycemic control, as evidenced by increases in FPG and A1C.

In addition, another study, conducted in Europe, has evaluated the combination of rosiglitazone maleate plus glimepiride in 172 patients with type 2 diabetes. In this 26-week, double-blind, placebo-controlled study, a statistically significant improvement in glycemic control (mean decrease in A1C of -0.006, $p = 0.03$) was observed in patients randomized to receive rosiglitazone maleate 4 mg once daily in combination with glimepiride 3 mg once daily ($n = 56$, mean baseline A1C of 0.082) compared to glimepiride alone ($n = 57$, mean baseline A1C of 0.079). (Note: Glimepiride 3 mg dosage strength is not available in Canada).

Table 7 Glycemic Parameters in Two 26-Week Combination Studies

Study #1	**Sulfonylurea[1]**	**Rosiglitazone maleate 1 mg twice daily + sulfonylurea**	**Rosiglitazone maleate 2 mg twice daily + sulfonylurea**
N	192	199	183
FPG (mmol/L)			
Baseline (mean)	11.5	11.3	11.4
Change from baseline (mean)	0.3	-0.9	-2.1
Difference from sulfonylurea alone (adjusted mean)	--	-1.3*	-2.4*
Responders (≥1.7 mmol/L decrease from baseline)	21%	38%	56%
A1C (ratio)			
Baseline (mean)	0.092	0.092	0.092
Change from baseline (mean)	0.002	-0.005	-0.009
Difference from sulfonylurea alone (adjusted mean)	--	-0.006*	-0.010*
Responders (≥0.007 decrease in ratio from baseline	19%	39%	60%
Goal (0.08 at week 26)	21%	35%	49%

Study #2	**Sulfonylurea[2]**	**Rosiglitazone maleate 2 mg once daily + sulfonylurea**	**Rosiglitazone maleate 4 mg once daily + sulfonylurea**
N	115	114	116
FPG (mmol/L)		12.3	
Baseline (mean)	11.6	-0.6	11.9
Change from baseline (mean)	1.3	-1.6*	-1.4
Difference from sulfonylurea alone (adjusted mean)	--	37%	-2.6*
Responders (≥1.7 mmol/L decrease from baseline)	13%		46%
A1C (ratio)			
Baseline (mean)	0.087	0.093	0.09
Change from baseline (mean)	0.006	0	-0.003
Difference from sulfonylurea alone (adjusted mean)	--	-0.006*	-0.008[3]
Responders (≥0.007 decrease in ratio from baseline)	6%	28%	29%
Goal (0.08 at week 26)	17%	25%	42%

1. Sulfonylureas include glyburide, glipizide and gliclazide.
2. Sulfonylurea include glyburide.
3. ≤0.0001 compared to sulfonylurea

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).

Cardiovascular Studies:
Two echocardiography studies in 437 type 2 diabetic patients (a 52-week study with rosiglitazone maleate 4 mg twice daily and a 26-week study with 8 mg once daily), designed to detect a change in left ventricular mass of 10% or more, showed no deleterious alteration in cardiac structure or function. Compared to placebo, there was a small, statistically significant increase in median plasma volume (1.8 mL/kg) in healthy volunteers treated with rosiglitazone 8 mg once daily for 8 weeks. See ADVERSE REACTIONS for experience concerning serious cardiovascular adverse events.

Patients with congestive heart failure (CHF) New York Heart Association (NYHA) Class I and II treated with rosiglitazone have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-controlled echocardiographic study was conducted in 224 patients with type 2 diabetes mellitus and NYHA Class I or II CHF (ejection fraction ≤ 45%) on background antidiabetic and CHF therapy. An independent committee conducted a blinded evaluation of fluid-related events (including congestive heart failure) and cardiovascular hospitalizations according to predefined criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were reported by investigators. Although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed with rosiglitazone treatment compared to placebo during the 52-week study (see Table 8).

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

Events	Placebo N = 114 n (%)	Rosiglitazone N = 110 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

Rosiglitazone in Combination with Insulin

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

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

There are no studies that have evaluated the safety or effectiveness of AVANDARYL® in combination with insulin.

In 26-week double-blind fixed dose studies, edema was reported with higher frequency in the rosiglitazone maleate plus insulin combination trials (insulin, 5.4%; and rosiglitazone maleate in combination with insulin, 14.7%). Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with rosiglitazone maleate (see WARNINGS AND PRECAUTIONS, Cardiovascular). In these studies, approximately 2.5% of the patients were enrolled with a presenting medical condition of congestive heart failure (NYHA Class I/II). Patients with NYHA Class III and IV heart failure were excluded from all clinical trials.

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

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

TOXICOLOGY

No animal studies have been conducted with AVANDARYL®. The following data are based on findings in studies performed with rosiglitazone maleate or glimepiride individually.

Rosiglitazone maleate

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=12.5μg.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
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.

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

Glimepiride

Teratogenic effects
Glimepiride did not produce teratogenic effects in rats exposed orally up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area). Glimepiride has been shown to be associated with intrauterine fetal death in rats when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

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

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

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

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PART III: CONSUMER INFORMATION

[Pr]AVANDARYL®
rosiglitazone maleate and glimepiride tablets

This leaflet is part III of a three-part "Product Monograph" for AVANDARYL® and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AVANDARYL®. 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:
AVANDARYL® (ah-VAN-duh-ril) is a medicine used in addition to diet and exercise to lower blood sugar in patients with type 2 diabetes (non-insulin dependent) when all other diabetes medicines taken orally (by mouth) have not lowered blood sugar enough or are not appropriate.

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

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

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

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

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

What it does:
AVANDARYL® combines two glucose-lowering medicines, rosiglitazone maleate (AVANDIA®) and glimepiride (Amaryl®), together in one tablet. These two medicines work together to help you achieve better blood sugar control. Rosiglitazone helps your body use its own insulin better by making the tissues more sensitive to insulin. The tissues are better able to "hear" the signals insulin sends out. That means the tissues will absorb sugar more easily. Glimepiride helps your body to release more of its own insulin. Together, these medicines keep the amount of sugar in your blood at a more normal level.

When it should not be used:
- If you have or have had heart problems or heart failure (the heart cannot pump enough blood to the body's or other organs), talk to your doctor. AVANDARYL® can cause your body to keep extra fluid (fluid retention), which can make some heart problems worse, lead to heart failure, swelling and weight gain.
- If you have Type 1 diabetes – this needs different treatment.
- If you are allergic to AVANDARYL®, any of its components, or other sulfonylurea or sulfonamide drugs.
- If you have serious liver problems.
- If you have diabetic ketoacidosis (dangerously high levels of ketones, which signals the body doesn't have enough insulin).
- If you are pregnant or breastfeeding. Other medicines are used to control your diabetes while you are pregnant or breastfeeding.

What the medicinal ingredient is:
AVANDARYL® tablets contain two active ingredients, rosiglitazone maleate (AVANDIA®) and glimepiride (Amaryl®), in one tablet.

What the nonmedicinal ingredients are:
lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, hypromellose 2910, magnesium stearate, titanium dioxide, macrogol (polyethylene glycol), and one or more of the following: yellow, red, or black iron oxides

What dosage forms it comes in:
rosiglitazone maleate/glimepiride tablets
4mg/1mg, 4mg/2mg, 4mg/4mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- AVANDARYL®, which contains rosiglitazone, 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)
- AVANDARYL® should not be used if you have or have had heart problems.

Before you use AVANDARYL®, talk to your doctor about other options to treat your diabetes.

Before you use AVANDARYL®, talk to your doctor or pharmacist about all your medical conditions, including if:

- you have experienced edema (swelling in the wrists, hands, feet or ankles).
- you have been diagnosed with angina (chest 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 kidney problems.
- you are taking nitrate medicines (such as nitroglycerin or isosorbide dinitrate).
- you have a type of diabetic eye disease called macular edema (swelling in the back of the eye).
- you have liver problems.
- you are breastfeeding.
- you are pregnant or planning to become pregnant.
- you are not near menopause but not ovulating (e.g., you are a patient with polycystic ovary syndrome), AVANDARYL® could make you ovulate again, which means you could get pregnant. Talk to your doctor about effective methods of birth control (e.g., hormonal contraceptive pills).
- you have a blood disease called G6PD-deficiency anemia.

AVANDARYL® may cause low blood sugar (hypoglycemia). Make sure you know what to do if your blood sugar gets too low (ask your doctor, pharmacist or diabetes educator). Teach your friends, co-workers, or family members what they can do to help you if you have low blood sugar.

Broken bones, usually in the hand, upper arm or foot, have been seen in people taking rosiglitazone, one of the active ingredients of AVANDARYL®. Talk to your doctor about the risk of fracture.

The safety and effectiveness of AVANDARYL® have not been established in children under 18 years of age, therefore AVANDARYL® is not recommended for use in these patients.

AVANDARYL® is not approved for use with insulin therapy, therefore AVANDARYL® is not recommended for use with insulin.

AVANDARYL® is not approved for use with metformin, therefore AVANDARYL® is not recommended for use with metformin.

INTERACTIONS WITH THIS MEDICATION

AVANDARYL® may affect how other medicines work, and some medicines may affect how AVANDARYL® works. Drugs that may interact with the two active ingredients in AVANDARYL® (rosiglitazone maleate and glimepiride) include acetylsalicylic acid (ASA), corticosteroids, diuretics (water pills), gemfibrozil (used to lower cholesterol and triglyceride levels in your blood), methotrexate (used to treat psoriasis and rheumatoid arthritis), non-steroidal anti-inflammatory drugs (NSAID), rifampin (used to treat tuberculosis), "sulfa drugs" (e.g. sulphonamides), warfarin, some antibiotics (e.g. clarithromycin, tetracycline) or beta-blockers (heart drug).

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

PROPER USE OF THIS MEDICATION

Usual dose:

The usual starting dose of AVANDARYL® may be 4 mg/1 mg, 4 mg/2 mg, or 4 mg/4 mg, depending on your previous treatment with rosiglitazone (AVANDIA®) and/or glimepiride (AMARYL®). Your doctor will decide on the dose of AVANDARYL® that is suitable for you.

AVANDARYL® should be taken by mouth once a day with a meal.

Your doctor may need to adjust your dose until your blood sugar is better controlled. AVANDARYL® can begin to work 1 or 2 weeks after you start taking it. It may take 2-3 months to see the optimal effects.

Test your blood sugar regularly as your doctor tells you.

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

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

Overdose:
Taking too much of any medicine can be dangerous.

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

Missed Dose:
Take the missed dose as soon as possible, unless it is almost time for your next dose. Do not take two doses at the same time.

Recommended clinical and laboratory tests while taking AVANDARYL®:

Your doctor may do additional blood sugar tests to see how well AVANDARYL® is working.

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

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Very common side effects (could affect more than one in 10 people):
- Edema (fluid retention or swelling) which could lead to or worsen heart failure. If you notice swelling in your extremities (arms and legs, hands and feet), an unusually rapid increase in weight, or if you experience unusual tiredness, trouble breathing or shortness of breath, call your doctor. These symptoms, although not specific, may signal heart problems or heart failure. Pay closer attention to these symptoms as fluid retention is common if you are using AVANDARYL®.

Common side effects (could affect up to one in 10 people):
- Anemia (low red blood cell count) which may make you feel very weak or tired.
- Chest pain (angina)
- Heart failure or pulmonary edema (fluid accumulation in the lungs). Symptoms of heart failure include shortness of breath, getting tired easily after light physical activity such as walking, unusual tiredness, waking up short of breath at night, swollen ankles or feet, and an unusually rapid increase in weight. Symptoms of fluid in the lungs are breathlessness, which may be very severe and usually worsens on lying down. Stop taking AVANDARYL® and call your doctor right away if you experience these symptoms.
- Stomach (gastrointestinal) symptoms such as nausea.
- 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. Total cholesterol is made up of "good cholesterol" (HDLc) and "bad cholesterol" (LDLc) and it is the balance of these that is more important than the total level. AVANDARYL®, does not affect the balance of good and bad cholesterol. If you have any concerns about your cholesterol levels, you should speak to your doctor.
- Low blood sugar (hypoglycemia). Dizziness, lack of energy, drowsiness, headache, trembling, sweating. or hunger may mean that your blood sugar is too low. This can happen if you skip meals, drink alcohol, use another medicine that lowers blood sugar, exercise (particularly hard or long), or if you have certain medical problems. Call your doctor if you feel that your symptoms of low blood sugar are uncomfortable.
- Increased weight. Tell your doctor if you gain a lot of weight in a short period of time.

Uncommon side effects (could affect up to one in 100 people):
- Mild allergic reactions may develop into more severe reactions with shortness of breath, chest tightness and in some cases low blood pressure which may present as lightheadedness. Therefore, if rash or hives, or any of the more serious symptoms occur, stop taking AVANDARYL® and call your doctor right away.
- Constipation
- Increased hunger

Rare side effects (could affect up to one in 1,000 people):
- Liver problems. If you experience nausea, vomiting, stomach pain, lack of appetite, tiredness, dark urine, light-coloured bowel movements, or yellowing of the skin, stop taking AVANDARYL® and call your doctor right away. Additionally, liver problems may result in the build-up of bile in the liver (cholestasis). Irritation or inflammation of the liver (hepatitis) may also occur and may lead to liver failure (failure of the liver to carry out its normal function).
- Blurred vision due to swelling (or fluid) in the back of the eye.

Very rare side effects (could affect up to one in 10,000 people):

- Allergic reactions, which may include hives or rash (which may be itchy), or more serious symptoms which may occur suddenly, such as swelling of the face, lips, mouth, tongue or throat (which may cause difficulty in swallowing or breathing). Stop taking AVANDARYL® and contact your doctor or other healthcare professional immediately if any of these occur.
- Stomach or intestinal (gastrointestinal) symptoms such as nausea, vomiting, pressure or pain in the stomach (or upper abdomen) and diarrhea.
- Decreases in certain types of blood cells (white blood cells and platelets), which may increase your risk of infection or bleeding.
- Decrease in the amount of sodium (salt) in your blood, which may present as weakness, fatigue or confusion if mild and as seizures (convulsions) if severe. If you have these symptoms, stop taking AVANDARYL® and call your doctor right away.
- Breakthrough bleeding (unexpected vaginal bleeding or spotting) while using oral contraceptives, or generally, if you experience any symptoms that persist or become troublesome, these should be discussed with your doctor.
- Skin reactions caused by sensitivity of the skin to light.

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

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

Symptom / effect		Talk with your doctor		Stop taking AVANDARYL® and call your doctor immediately
		Only if severe	In all cases	
Very Common	Fluid retention or swelling in extremities (arms and legs, hands and feet) without signs of heart failure or fluid in the lungs (see below).		✓	
Common	Low red blood cell count (anemia): feeling very weak or tired		✓	
Common	Low blood sugar levels (hypoglycemia): Dizziness, lack of energy, drowsiness, headache, trembling or sweating, or hunger	✓		
Common	Heart failure or fluid in the lungs (pulmonary edema): trouble breathing or shortness of breath, getting tired easily after light physical activity, unusual tiredness, waking up short of breath at night, an unusually rapid increase in weight. Fluid may also cause swollen ankles or feet			✓
Common	Chest pain (angina)		✓	
Uncommon	Allergic reactions: shortness of breath, chest tightness, low blood pressure, light-headedness, hive or rash. The following symptoms are considered **very rare**: 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 AVANDARYL® and call your doctor immediately
		Only if severe	In all cases	
Rare	Liver problems: nausea, vomiting, stomach pain, lack of appetite, tiredness, dark urine, light-coloured bowel movements, or yellowing of the skin			✓
Rare	Blurred vision or decreased vision (which may be due to swelling (or fluid) in the back of the eye).			✓
Very rare	Allergic reaction: 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)			✓
Very rare	Decrease in certain types of blood cells (white blood cells and platelet)		✓	
Very rare	Weakness, fatigue, confusion, seizure (convulsion)			✓

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

HOW TO STORE IT

Store AVANDARYL® at room temperature (15°C to 30°C), out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

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

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

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.gsk.ca or by contacting the sponsor,
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This leaflet was prepared by GlaxoSmithKline Inc.

Last revised: March 1, 2011