

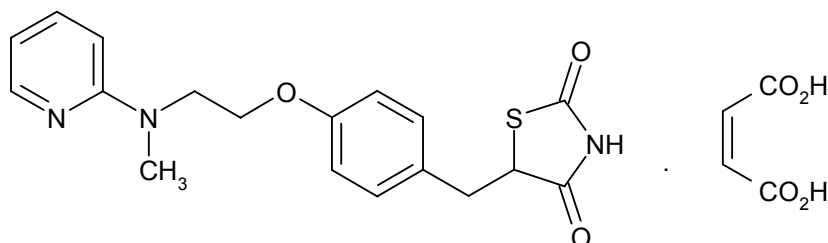
## PRODUCT INFORMATION

### AVANDIA® (rosiglitazone)

The use of AVANDIA is not recommended in patients with known ischaemic heart disease, particularly in those taking nitrates. AVANDIA has been shown to be associated with an increased risk of myocardial ischaemia (angina, infarction) in pooled short-term clinical studies compared to combined active/placebo control (2.00% versus 1.53%, respectively), particularly in those who needed several antidiabetic drugs or nitrates. See **Precautions**.

#### NAME OF THE DRUG

AVANDIA (rosiglitazone maleate) is an oral antidiabetic agent, chemically designated as ( $\pm$ )-5-[[4-[2-(methyl-2-pyridinylamino) ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (*Z*)-2-butenedioate (1:1). The structural formula is:



Molecular weight: 473.52 (357.44 free base)

CAS number : 0155141-29-0

#### DESCRIPTION

Rosiglitazone maleate is a white to off-white solid with a melting range of 122° to 123°C. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

AVANDIA tablets contain sodium starch glycollate, hypromellose, microcrystalline cellulose, lactose and magnesium stearate as excipients. The film coat contains hypromellose, lactose, macrogol 3000, titanium dioxide, glycerol triacetate and the following colouring agents: 2mg tablet: iron oxide red (CI77491); 4mg tablet: purified talc, iron oxide yellow (CI77492) and iron oxide red (CI77491); 8mg tablet: iron oxide red (CI77491).

#### PHARMACOLOGY

AVANDIA is a selective and potent agonist at the PPAR $\gamma$  (peroxisomal proliferator activated gamma) nuclear receptor and is a member of the thiazolidinedione class of antidiabetic agents.

AVANDIA improves glycaemic control by improving insulin sensitivity at key sites of insulin resistance namely adipose tissue, skeletal muscle and liver. Insulin resistance is known to play a major role in the pathophysiology of type 2 diabetes. Thus, AVANDIA improves metabolic control by lowering blood glucose, circulating insulin and free fatty acids.

The antihyperglycaemic activity of AVANDIA has been demonstrated in a number of rodent models of type 2 diabetes. In addition, AVANDIA preserved  $\beta$ -cell function as shown by increased pancreatic islet mass and insulin content and prevented the development of overt hyperglycaemia in rodent models of type 2 diabetes. AVANDIA has also been shown to significantly delay the onset of renal dysfunction and systolic hypertension. AVANDIA did not stimulate pancreatic insulin secretion or induce hypoglycaemia in rats and mice.

## Pharmacokinetics

### Absorption

AVANDIA is rapidly and completely absorbed after oral administration, with negligible first pass metabolism. Absolute bioavailability of AVANDIA following both a 4 mg and an 8 mg oral dose is approximately 99%. Plasma concentrations of AVANDIA peak at around 1 hour after dosing and are approximately dose proportional over the therapeutic dose range.

Administration of AVANDIA with food resulted in no change in overall exposure (AUC), although a small decrease in C<sub>max</sub> (approximately 20-28%) and a delay in T<sub>max</sub> (1.75 h) were observed when compared to dosing in the fasted state. These small changes are not clinically significant and therefore, it is not necessary to administer AVANDIA at any particular time in relation to meals. The absorption of AVANDIA is not affected by increases in gastric pH.

### Distribution

The volume of distribution of AVANDIA is approximately 0.184 L/kg and total plasma clearance around 3 L/h in healthy volunteers. AVANDIA is approximately 99.8% bound to plasma protein, primarily albumin. Concentration or age does not influence plasma protein binding of AVANDIA. There is no evidence for unexpected accumulation of rosiglitazone after once daily or twice daily dosing.

### Metabolism

Metabolism of AVANDIA is extensive with no parent compound being excreted unchanged. The major routes of metabolism are N-demethylation and hydroxylation, followed by conjugation with sulphate and glucuronic acid. The metabolites of AVANDIA are not considered to have any clinical relevance.

*In vitro* data demonstrate that AVANDIA is predominantly metabolised by Cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing only as a minor pathway. In *in vitro* studies, rosiglitazone caused a moderate inhibition of CYP2C8 and minor inhibition of CYP2C9. Significant inhibition of these enzymes is unlikely to occur at therapeutic doses. In addition, there is no significant *in vitro* inhibition of CYP1A2, 2A6, 2C19, 2D6, 2E1, 3A or 4A with AVANDIA, therefore there is a low probability of significant metabolism-based interactions with drugs metabolised by these P450 enzymes (see **Interactions**).

A study conducted in ten normal healthy volunteers showed that gemfibrozil (an inhibitor of CYP2C8) administered as 600 mg twice daily, increased rosiglitazone exposure two-fold at steady state (see **Dosage and Administration, Interactions**).

A study conducted in ten normal healthy volunteers showed that rifampicin (an inducer of CYP2C8) administered as 600 mg daily, decreased rosiglitazone exposure to one third (see **Dosage and Administration, Interactions**).

## Excretion

The terminal elimination half-life of AVANDIA is approximately 3 to 4 hours. The major route of excretion is the urine with approximately two-thirds of the dose being eliminated by this route. Faecal elimination accounts for approximately 25% of dose.

In the pooled population pharmacokinetic analysis, there were no marked differences in the pharmacokinetics of AVANDIA between males and females, or between elderly and non-elderly patients.

In patients with moderate to severe (Child-Pugh B/C) hepatic disease, unbound C<sub>max</sub> and AUC were 2- and 3-fold higher in patients with hepatic impairment as a result of decreased plasma protein binding and reduced clearance of AVANDIA (see **Dosage and Administration**).

There are no clinically significant differences in the pharmacokinetics of AVANDIA in patients with renal impairment or end stage renal disease on chronic dialysis. No dosage adjustment is required in these patients.

## CLINICAL TRIALS

Evidence to support the efficacy of AVANDIA in the treatment of type 2 diabetes was obtained in several multi-centre, double-blind studies. These studies, investigated the use of AVANDIA as monotherapy, and in combination with sulfonylureas (SUs) and metformin.

In clinical studies with AVANDIA given as monotherapy at doses of 4 to 8mg/day, the glucose lowering effects are gradual in onset and are not associated with hypoglycaemia. Reductions in fasting plasma glucose are observed from 1 week of initiation of therapy, although the full therapeutic effect may take 6-8 weeks to occur. While improvement in glycaemic control was associated with increases in weight, changes were highly variable. In 26-week clinical trials, the mean weight gain in patients treated with AVANDIA was 1.2 kg (range: -11.6 to 12.7) (4 mg daily) and 3.5 kg (range: -6.8 to 13.9) (8 mg daily) when administered as monotherapy, 0.7 kg (range: -6.8 to 9.8) (4 mg daily) and 2.3 kg (range: -5.4 to 13.1) (8 mg daily) when administered in combination with metformin and 1.8 kg (range: -5 to 11.5) (4 mg daily) when administered in combination with sulfonylurea. In a 52-week glibenclamide-controlled study, there was a mean weight gain of 1.75 kg (range: -7.0 to 16.0) and 2.95 kg (range: -11.0 to 22.0) for patients treated with 4 mg and 8 mg of AVANDIA daily, respectively, versus 1.9 kg (range: -11.5 to 12.2) in glibenclamide-treated patients. 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.

In type 2 diabetes, long term and sustained improvements in glycaemic control (FPG and HbA<sub>1c</sub>) have been demonstrated with AVANDIA given once or twice daily as monotherapy or in combination with other antidiabetic agents (sulfonylureas, metformin or insulin). In two studies, AVANDIA produced significantly greater reductions in FPG than glibenclamide after 52 weeks of treatment. AVANDIA treatment has been associated with clinically significant reductions in fasting and postprandial plasma glucose levels and in glycated haemoglobin. The improvement in glycaemic control was maintained throughout the duration of the studies (up to 18 months).

**Renal impairment:** In a controlled clinical trial, AVANDIA (4 or 8 mg daily) used in combination with insulin and/or a sulfonylurea was effective in reducing glycaemia in patients with type 2 diabetes and mild to severe (not dialysis dependent) renal impairment. There were no additional safety concerns noted in these renally-impaired patients compared to type 2 diabetic patients without renal impairment.

Consistent with the mechanism of action of AVANDIA, enhanced glycaemic control is accompanied by clinically significant decreases in serum insulin and C-peptide levels. There are also reductions in proinsulin and 32, 33 split proinsulin, which are believed to correlate with cardiovascular risk factors. Significant decreases in free fatty acids are a key feature of AVANDIA treatment.

Patients with lipid abnormalities were not excluded from clinical trials of AVANDIA. As monotherapy, AVANDIA was associated with dose-ordered increases in total cholesterol (TC), LDL-cholesterol and HDL-cholesterol and decreases in free fatty acids. The increase in LDL occurred during the first 1 to 2 months of therapy with AVANDIA, plateauing thereafter. In contrast, HDL continued to rise over time. As a result the TC/HDL ratio was unchanged after 12 months treatment, with a subsequent reduction from baseline after longer term treatment. The pattern of LDL and HDL changes following therapy with AVANDIA in combination with metformin or sulfonylureas was generally similar in magnitude and time course to those seen with AVANDIA as monotherapy. The changes seen in triglycerides during therapy with AVANDIA were variable.

**Table 1. Summary of median lipid changes in a 52 week glibenclamide-controlled monotherapy study (020)**

	Glibenclamide	Rosiglitazone 8 mg daily
<b><i>Free Fatty Acids</i></b>		
N	168	145
Baseline median (mmol/L)	0.92	0.93
% Change	-9.7%	-24.7%
<b><i>LDL</i></b>		
N	160	133
Baseline median (mmol/L)	3.68	3.63
% Change	-3.3%	+7.3%
<b><i>HDL</i></b>		
N	170	145
Baseline median (mmol/L)	1.18	1.19
% Change	+8.0%	+17.4%
<b><i>TC/HDL</i></b>		
N	184	170
Baseline median	4.90	4.76
Difference from Baseline	-0.33	-0.08

### ***Monotherapy***

A total of 2,526 patients were treated with AVANDIA as monotherapy in six randomised, double-blind, placebo/active-controlled studies. These studies ranged in duration from 8 weeks to 52 weeks and included patients with a range of severity of diabetes. Although a specific study of AVANDIA in diet and exercise-treated patients has not been conducted, a total of 736 patients previously treated with diet and exercise alone received AVANDIA as monotherapy in the clinical trial programme.

In a 26-week double-blind, placebo-controlled trial in type 2 diabetic patients with inadequate glycaemic control, all doses of AVANDIA resulted in a significant improvement in glycaemic control relative to baseline and placebo (Table 2).

When AVANDIA was dosed at 4 mg bd, 70% of patients responded with a  $\geq 1.7$  mmol/L reduction from baseline in FPG compared to 58% treated with 8 mg od, 54% with 2 mg bd, 45% with 4 mg od and 19% with placebo.

When administered at the same total daily dose, AVANDIA was generally more effective when administered in divided doses twice daily compared to once daily doses. The effect on HbA1c, however, was not statistically significant between 4 mg once daily and 2 mg twice daily.

**Table 2. Improvement in metabolic control in a 26 week placebo-controlled monotherapy study**

<b>STUDY 024</b>	<b>Placebo</b>	<b>AVANDIA A 4 mg od</b>	<b>AVANDIA A 2 mg bd</b>	<b>AVANDIA A 8 mg od</b>	<b>AVANDIA 4 mg bd</b>
<b>N</b>	173	180	186	181	187
<b>FPG (mmol/L)</b>					
Baseline	12.5	12.7	12.5	12.7	12.7
Week 26	12.0	11.4	10.5	10.3	9.6
Difference from placebo (adjusted mean)	-	-1.73*	-2.41*	-2.73*	-3.46*
<b>HbA1c (%)</b>					
Baseline (mean)	8.93	8.91	8.87	8.94	9.04
Week 26 (mean)	9.72	8.93	8.74	8.62	8.37
Difference from placebo (adjusted mean)	-	-0.77*	-0.93*	-1.10*	-1.45*

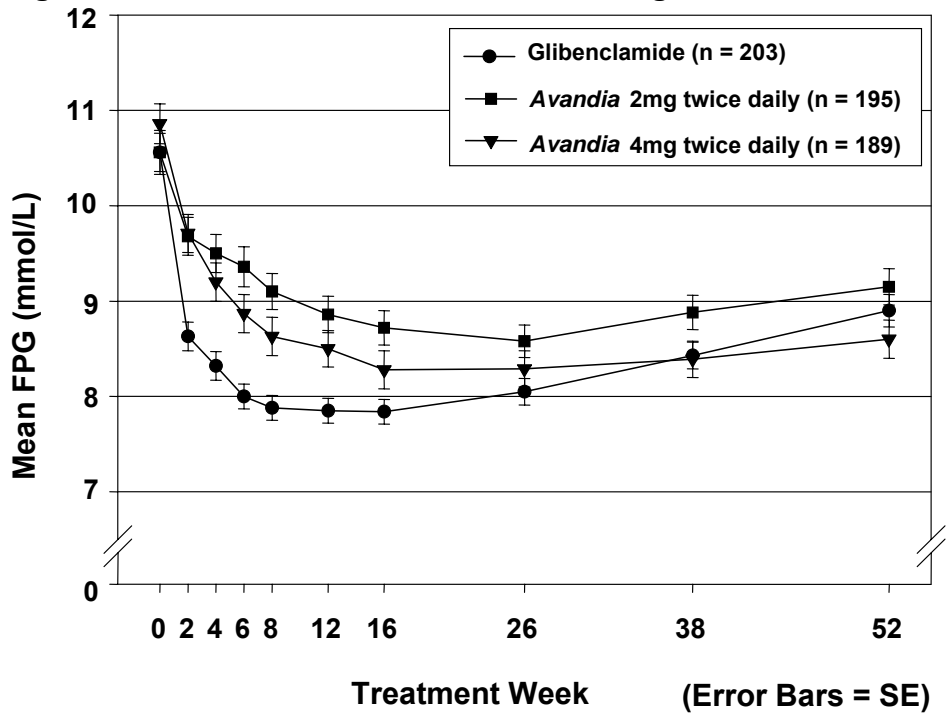
\* $<0.0001$  compared to placebo

In a second 26-week double-blind, placebo-controlled study in diabetic patients with inadequate glycaemic control, a statistically significant improvement in HbA1c of 1.2% and 1.5% and in FPG of 3.2 mmol/L and 4.2 mmol/L was observed with AVANDIA when administered at 2 mg bd and 4 mg bd, respectively, compared with placebo.

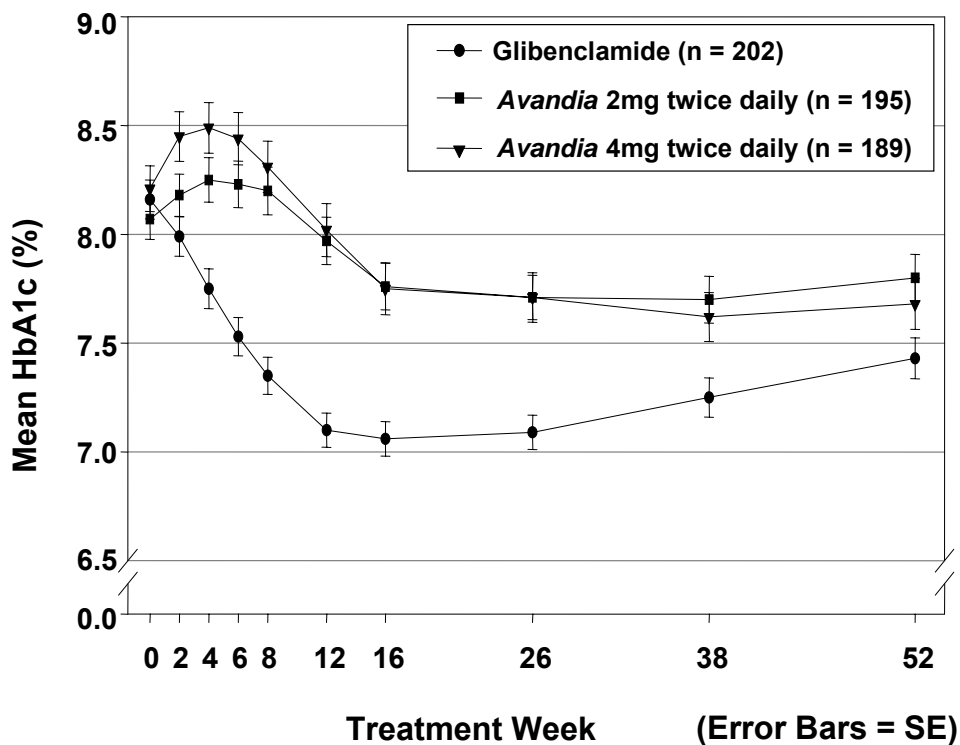
When AVANDIA was dosed at 4 mg bd, 64% of patients responded with a 1.7 mmol/L reduction from baseline in FPG compared to 54% with 2 mg bd and 16% with placebo.

In a 52-week double-blind, active-controlled study which enrolled 587 type 2 diabetic patients, AVANDIA 2 mg bd and 4 mg bd was compared to glibenclamide. Patients in all three treatment groups displayed a statistically significant improvement in glycaemic control. According to the protocol-defined definition of equivalence, AVANDIA 4 mg bd was as effective as glibenclamide in reducing HbA1c and resulted in significantly greater reductions in FPG than glibenclamide after 52 weeks of treatment. At the end of week 52, the reduction from baseline in FPG and HbA1c was 2.3 mmol/L and 0.53% with 4 mg bd AVANDIA; 1.4 mmol/L and 0.27% with 2 mg bd AVANDIA; 2.0 mmol/L and 0.72% with glibenclamide. The improvement in glycaemic control observed at week 26 with AVANDIA 4 mg bd was maintained throughout the second 26-week period of the study. In patients treated with AVANDIA, C-peptide, insulin and split products of insulin were significantly reduced, compared to an increase in the glibenclamide-treated patients.

**Figure 1 Mean FPG over time in a 52 week glibenclamide-controlled study**



**Figure 2 Mean HbA1c over time in a 52 week glibenclamide-controlled study**



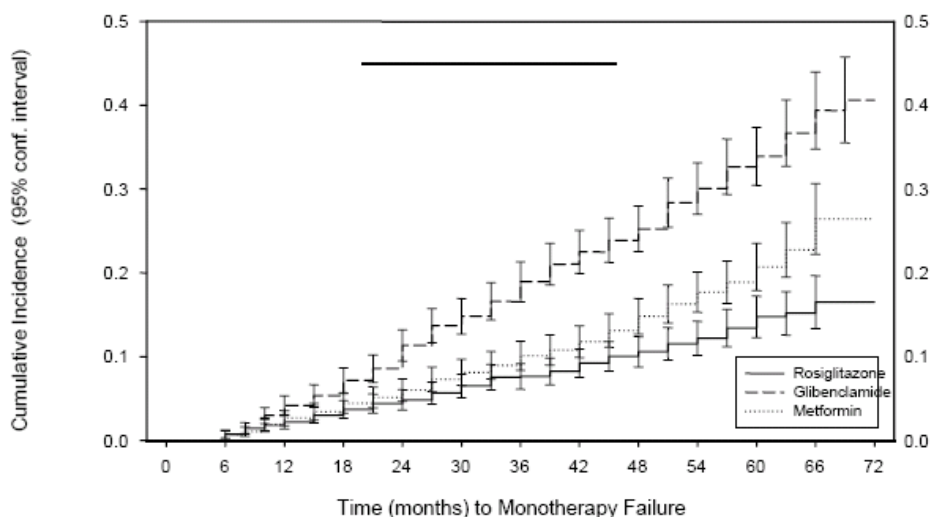
ADOPT (Study Protocol BRL-049653-048) was a randomised, double-blind, parallel group, active comparator controlled efficacy and safety trial of 4 to 6 years duration (median 4 years). The study was conducted in 473 centres (of which 467 enrolled at least one subject) in 17 countries in North America and Europe. The inclusion criteria included:

- subjects with Type 2 Diabetes Mellitus (T2DM), non-insulin dependent diabetes mellitus or NIDDM, as defined by the criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus;
- male or female adult subjects 30 to 75 years of age, inclusive, at the time of screening; subjects diagnosed for  $\leq 3$  years with T2DM subjects with an FPG range of 7.0 to 13.3 mmol/L at pre-screening and screening;
- subjects who had not been treated with oral or parenteral glucose-lowering therapy (with the following exceptions - insulin use during gestational diabetes mellitus; short term ( $\leq 1$  month) insulin use to maintain glycaemic control for hospitalization or medical procedure/intervention;  $\leq 2$  weeks of oral hypoglycaemic agent (OHA)  $\geq 2$  weeks prior to screening or  $> 2$  weeks – 1 month OHA  $\geq 2$  months prior to screening). The study was thus a first line monotherapy trial.

The study treatments were: rosiglitazone 4 mg morning or b.d.; or metformin 500 mg to 2,000mg daily or glibenclamide 2.5 mg to 15mg daily. The primary efficacy outcome measure: time to monotherapy failure defined as: FPG $>10$  mmol/L on consecutive occasions following at least 6 weeks of dosing with the maximum tolerated dose of study medication; or monotherapy failure as judged by the independent adjudication committee. A total of 4,127 subjects was included in the intention to treat population: 1,393 in the rosiglitazone group, 1,337 in the glibenclamide group and 1,397 in the metformin group.

The study results are presented below:

**Figure 3 Time to Monotherapy Failure**



Participants at Risk	0	6	12	18	24	30	36	42	48	54	60	66	72
Rosiglitazone	1393	1207	1078	957	844	781	617	518	418	311	218	118	7
Glibenclamide	1337	1114	958	781	617	518	418	311	218	118	78	8	8
Metformin	1397	1205	1076	950	818	618	518	418	311	218	118	12	12

As shown above, rosiglitazone showed a significantly longer time to monotherapy failure compared with metformin and glibenclamide, during the course of the study. A greater time to monotherapy failure is not necessarily indicative of long term outcomes nor does it suggest an alteration in the natural history of the disease.

At 4 years, the adjusted mean FPG reduction from baseline was significantly greater with rosiglitazone compared with glibenclamide (treatment difference -0.97 mmol/L{-17.4 mg/dL },  $p < 0.0001$ ) and with metformin (treatment difference -0.55 mmol/L{-9.8 mg/dL },  $p < 0.0001$ ).

These efficacy results need to be interpreted in the light of safety signals in generally healthy patients such as an association between the administration of rosiglitazone and continuous weight gain (see **Adverse Reactions**, Metabolic and Nutritional), fractures in women (especially of the lower limb), oedema and lipid effects.

**Table 3: On-Therapy AEs Reported in ADOPT by  $\geq 2.0\%/100$  Patient Years in Any Treatment Group**

Preferred Term	Number of Subjects, n %					
	RSG N=1456 PY=4953.8		GLY/GLIB N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY
<b>Subjects who experienced at least one On-Therapy AE</b>	1338 (91.9)	27.0	1321 (91.7)	31.1	1341 (92.2)	27.3
Nasopharyngitis	312 (21.4)	6.3	291 (20.2)	6.9	323 (22.2)	6.6
Back pain	250 (17.2)	5.1	209 (14.5)	4.9	261 (18.0)	5.3
Arthralgia	245 (16.8)	5.0	205 (14.2)	4.8	208 (14.3)	4.2
Hypertension	216 (14.8)	4.4	253 (17.6)	6.0	297 (20.4)	6.1
Upper respiratory tract infection	212 (14.6)	4.3	212 (14.7)	5.0	231 (15.9)	4.7
Bronchitis	190 (13.1)	3.8	151 (10.5)	3.6	172 (11.8)	3.5
Edema peripheral	188 (13.0)	3.8	118 (8.2)	2.8	100 (6.9)	2.0
Pain in extremity	183 (12.6)	3.7	151 (10.5)	3.6	175 (12.0)	3.6
Influenza	176 (12.1)	3.6	153 (10.6)	3.6	203 (14.0)	4.1
Hypercholesterolemia	172 (11.8)	3.5	108 (7.5)	2.6	107 (7.4)	2.2
Cough	167 (11.5)	3.4	145 (10.1)	3.4	179 (12.3)	3.7
Headache	162 (11.1)	3.3	146 (10.1)	3.4	186 (12.8)	3.8
Urinary tract infection	147 (10.1)	3.0	110 (7.6)	2.6	127 (8.7)	2.6
Hyperlipidemia	145 (10.0)	2.9	76 (5.3)	1.8	79 (5.4)	1.6
Muscle spasms	145 (10.0)	2.9	54 (3.8)	1.3	96 (6.6)	2.0
Fatigue	141 (9.7)	2.9	123 (8.5)	2.9	176 (12.1)	3.6
Hypoglycemia	141 (9.7)	2.9	551 (38.2)	13.0	168 (11.6)	3.4
Sinusitis	138 (9.5)	2.8	131 (9.1)	3.1	139 (9.6)	2.8
Osteoarthritis	136 (9.3)	2.8	96 (6.7)	2.3	102 (7.0)	2.1
Dizziness	129 (8.9)	2.6	122 (8.5)	2.9	135 (9.3)	2.8
Diarrhea	125 (8.6)	2.5	137 (9.5)	3.2	334 (23.0)	6.8
Depression	114 (7.8)	2.3	113 (7.8)	2.7	107 (7.4)	2.2
Nausea	114 (7.8)	2.3	99 (6.9)	2.3	170 (11.7)	3.5
Shoulder pain	98 (6.7)	2.0	81 (5.6)	1.9	88 (6.1)	1.8

a. Note: Sorted by frequency of adverse events in RSG group.

b. Data Source: Table 8.2.4.1.1

At 48 months, total cholesterol, HDL-cholesterol, and LDL-cholesterol were higher in the rosiglitazone group compared with both control groups, and cholesterol/HDL-cholesterol ratio was higher in the rosiglitazone group than the metformin group. In comparison with metformin, although HDL-cholesterol was raised to a greater degree with rosiglitazone, the Total Cholesterol/ HDL-cholesterol ratio was poorer.

**Table 4: Lipid results for the three treatment therapies in ADOPT study**

	RSG	GLY/Glibenclamide	MET
Total Cholesterol (mg/dL)*	193.7	186.4	184.5
LDL (mg/dL)*	102.5	98.5	95.2
HDL (mg/dL)*	51.3	48.3	49.9
Total Cholesterol/HDL-cholesterol ratio**	3.96	4.0	3.83

\* Geometric Mean at Month 48-Data log-transformed

\*\* Raw Mean at Month 48

**Combination therapy with Metformin or Sulfonylureas**

Five well-controlled double-blind studies of 26 weeks duration assessed the efficacy of AVANDIA in combination with metformin or SUs. A total of 338 type 2 diabetic patients were treated concomitantly with AVANDIA and metformin and a total of 726 patients were treated concomitantly with AVANDIA and an SU. As a consequence of different but complementary mechanisms of action, combination therapy of AVANDIA with metformin or an SU resulted in additive improvements in glycaemic control in type 2 diabetic patients. The dose response relationship for efficacy was similar to that seen in monotherapy.

Improvements in metabolic control observed in two studies when AVANDIA was used in combination with a near maximal dose (2.5 g/day) metformin are displayed in Table 5.

**Table 5: Improvement in metabolic control in patients receiving AVANDIA plus metformin**

	AVANDIA 4mg od + metformin N=116	AVANDIA 8mg od + metformin N=110	AVANDIA 4mg bd + metformin N=103
Change in FPG versus metformin alone	-2.2 mmol/L	-2.9 mmol/L	-3.1 mmol/L
Change in HbA1c versus metformin alone	-1.0%	-1.2%	-0.8%
% of patients with FPG reduction $\geq$ 1.7mmol/L	45%	60%	67%

Similarly, investigation of AVANDIA in three studies in combination with SU demonstrated that combination therapy with AVANDIA 2 mg twice daily resulted in significant decreases of up 1.4% in HbA1c and of up 3.1 mmol/L in FPG compared to SU alone.

**INDICATIONS**

AVANDIA is indicated for the treatment of Type 2 diabetes mellitus (non-insulin dependent diabetes mellitus).

AVANDIA may be used in patients inadequately controlled by diet and exercise:

- (i). As monotherapy,
- (ii). In dual combination therapy with metformin or sulfonylureas

## CONTRAINDICATIONS

Use of rosiglitazone is contraindicated in patients:

- with hypersensitivity to rosiglitazone maleate or any of the listed excipients.
- with NYHA Class I to IV heart failure, or history of cardiac failure (see **Precautions**).
- experiencing an Acute Coronary Syndrome (unstable angina, NSTEMI and STEMI) (see **Precautions**).

## PRECAUTIONS

### General

AVANDIA is effective only in the presence of insulin and should not be used in type 1 diabetes mellitus.

As a consequence of improving insulin sensitivity, AVANDIA treatment in premenopausal anovulatory patients with insulin resistance (eg. patients with polycystic ovary syndrome) may result in resumption of ovulation. In these patients adequate contraception should be recommended to avoid the risk of pregnancy.

Long term studies on morbidity (including cardiovascular effects) and mortality outcomes are not yet available. AVANDIA should not be prescribed to lower cardiovascular risk.

Premenopausal women have received AVANDIA during clinical studies. Although hormonal imbalance has been seen in preclinical studies (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**), no significant adverse experiences associated with menstrual disorders have been observed. If unexpected menstrual dysfunction occurs the benefits of continued therapy should be reviewed.

### Hypoglycaemia

Patients taking rosiglitazone may be at risk of dose-related hypoglycaemia if receiving combination regimens that contain a sulfonylurea. A reduction in the dose of the concomitant agent may be necessary.

### Combination with Insulin

AVANDIA is not indicated for use with insulin.

An increased incidence of cardiac failure has been observed in clinical trials when thiazolidinediones are used in combination with insulin. Insulin and rosiglitazone are both associated with fluid retention, concomitant administration may increase the risk of oedema and could increase the risk of ischaemic heart disease.

### Congestive Heart Failure

AVANDIA, like other thiazolidinediones can cause or exacerbate congestive heart failure (CHF) in some patients. After initiation of AVANDIA, and after dose increases, patients should be monitored for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnoea, and/or oedema). If these signs and symptoms develop and CHF is diagnosed AVANDIA should be discontinued. The patient's heart failure should be evaluated and managed according to current standards of care. The risk of cardiac failure is significantly increased when rosiglitazone is used with more than one antidiabetic agent or insulin – AVANDIA is not indicated for use with insulin.

Use of AVANDIA in patients with NYHA Class I to IV heart failure or history of heart failure is contraindicated (see **Contraindications**).

Patients experiencing acute coronary syndromes (ACS) have not been studied in rosiglitazone controlled clinical trials. Since patients experiencing ACS are at an increased risk of developing heart failure, and in view of the potential for rosiglitazone to cause or exacerbate heart failure, initiation of AVANDIA in patients experiencing an acute coronary event is contraindicated. Furthermore, AVANDIA should be discontinued during the acute phase.

### **Myocardial Ischaemia**

AVANDIA has been shown to be associated with an increased risk of myocardial ischaemia (angina, infarction) in pooled short-term clinical studies (see below). AVANDIA is therefore not recommended for patients with known ischaemic heart disease (IHD), particularly those who are currently being treated with nitrates. There are limited clinical trial data in patients with peripheral arterial disease therefore, as a precaution, the use of rosiglitazone is not recommended in these patients.

In a retrospective analysis of 42 clinical trials (mean duration 6 months), AVANDIA was associated with an increased incidence of myocardial ischaemia compared to combined active/placebo control (2.00% versus 1.53%, respectively). Myocardial ischaemic events included angina pectoris, angina pectoris aggravated, unstable angina, cardiac arrest, chest pain, coronary artery occlusion, dyspnea, myocardial infarction, coronary thrombosis, myocardial ischaemia, coronary artery disease, and coronary artery disorder. This risk was highest in patients for whom AVANDIA was added to established insulin therapy (See **Precautions, Combination with Insulin and Adverse Events**), and in patients receiving nitrates for known coronary heart disease (CHD), [rosiglitazone 43 events/323 nitrate users (13.31%) v/s comparators 16 events/223 nitrate users (7.17%)]. Most of the nitrate users had established coronary heart disease. Patients with known coronary heart disease who were not on nitrate therapy, had no increased risk of myocardial ischaemic events with AVANDIA versus comparator [rosiglitazone 47 events/886 (5.30%) v/s comparators 33 events/622 (5.31%)]. Patients with no pre-existing CHD had no increased risk of myocardial ischaemic events with rosiglitazone versus comparator [rosiglitazone 81 events/7395 (1.1%) v/s comparators 36 events/4788 (0.75%)].

There was a trend to higher relative and absolute numbers of ischaemic events when rosiglitazone was added to metformin and a sulfonylurea. No statistically significant difference in risk was observed for AVANDIA compared to active control (metformin and/or sulfonylurea) in this retrospective analysis (1.90% v/s 2.36%, respectively) or in 2 large long-term studies (mean duration 3 to 4 years) when AVANDIA was used as monotherapy or as add-on (second drug) therapy. A non-significant trend was noted for AVANDIA to be associated with acute myocardial ischaemia when used in dual therapy as a second agent.

In ADOPT, a 4 to 6 year study of glycaemic control with monotherapy in recently diagnosed patients with T2DM, in which patients with any class of heart failure, unstable or severe angina, or uncontrolled hypertension were ineligible, the incidence rates for myocardial ischaemia for patients taking monotherapy rosiglitazone, glibenclamide or metformin were comparable (see ADVERSE EVENTS). Further, comparable rates of myocardial ischaemic events were observed among all 3 treatment groups in patients who had received prior nitrates or had received nitrates during the on therapy trial period up to an event (rosiglitazone 8 events/74 nitrate users; 10.8% v/s metformin 12 events/89 nitrate users; 13.5% v/s glibenclamide 9 events/76 nitrate users 11.8%).

Thiazolidinediones have not yet been shown to have beneficial effects on macrovascular risks in patients with type 2 diabetes mellitus.

Type 2 diabetes is a major risk factor for coronary heart disease and adverse outcomes following a myocardial ischaemic event. Thus, independent of the choice of antidiabetic agent, cardiovascular risk factors should be identified and corrective measures taken where possible. See also **Adverse Events, Cardiac Disorders**.

### **Triple Oral therapy**

The use of a thiazolidinedione in combination with metformin and a sulfonylurea may be associated with increased risks for fluid retention and heart failure, as well as hypoglycaemia. Triple oral therapy with rosiglitazone, metformin and a sulfonylurea is therefore not indicated.

### **Fluid Retention**

Fluid retention may occur. Signs and symptoms of fluid retention, including weight gain should be monitored. The possible contribution of fluid retention to weight gain should be individually assessed.

In controlled clinical trials of patients with type 2 diabetes, mild to moderate oedema which was generally dose-related was reported in patients treated with AVANDIA.

### **Monitoring of liver function:**

In clinical trials with AVANDIA, encompassing 2492 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevations of ALT levels. In post-marketing experience with AVANDIA there have been rare reports of hepatocellular dysfunction, primarily evidenced by elevated hepatic enzymes. Causality has not been established. However, it is recommended that patients treated with AVANDIA undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with AVANDIA in all patients. Therapy with AVANDIA should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5X upper limit of normal).

Patients with mildly elevated liver enzymes (ALT levels one to 2.5X upper limit of normal) at baseline or during therapy with AVANDIA should be evaluated to determine the cause of the liver enzyme elevation. If at any time ALT levels increase to >3X upper limit of normal in patients on therapy with AVANDIA, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with AVANDIA should be discontinued.

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

### **Effects on Bone**

In a 4 to 6 year study of glycaemic control with monotherapy in recently diagnosed patients with Type 2 diabetes mellitus, an increased incidence of bone fracture was noted in female patients taking rosiglitazone (9.3%, 2.7 patients per 100 patient years) vs metformin (5.1%, 1.5 patients per 100 patient years) or glibenclamide (3.5%, 1.3 patients per 100 patient years). The majority of the fractures in the females who received rosiglitazone were reported in the upper arm, hand and foot. The risk of fracture should be considered in the care of patients, especially female patients, treated with rosiglitazone, and attention should be given to assessing and maintaining bone health according to current standards of care.

### **Eye Disorder**

Very rare post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with rosiglitazone. Many of these patients reported concurrent peripheral oedema. In some cases the visual events resolved or improved following discontinuation of the drug. Prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity.

### **Carcinogenicity, mutagenicity and impairment of fertility**

Two-year carcinogenicity 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 tumours (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.

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.

There were no effects on mating performance or on fertility of male rats following treatment with rosiglitazone at exposures greater than 100 times those anticipated clinically (based on AUC). However, following long-term treatment of male rats with rosiglitazone, reduced testicular size was noted at exposures approximately twice the maximum anticipated clinical exposure and this was associated with seminiferous tubular atrophy at exposures approximately ten times the maximum anticipated clinical exposure (based on AUC).

Rosiglitazone lowered plasma levels of progesterone and oestradiol, altered oestrus cyclicity and reduced fertility of female rats but only at exposures to rosiglitazone greater than 20 times anticipated clinical exposure (based on AUC). In monkeys, rosiglitazone diminished the follicular rise in serum oestradiol with consequential reduction in the luteinising hormone surge, lower luteal phase progesterone levels and irregular menstrual cycles at exposures 2.7 times anticipated clinical exposure (based on AUC).

### **Patients with Familial Adenomatous Polyposis (FAP)**

Treatment of Min mice with rosiglitazone or several other thiazolidinediones led to an increased incidence of tumours in the large intestine. Min mice carry a mutation in the Apc gene and have been used as a model of human Familial Adenomatous Polyposis (FAP). Whilst the relevance of these findings are uncertain, AVANDIA should not be used in patients known or suspected to have a mutation in the Apc gene (eg. FAP) due to a potentially increased risk of enhanced adenoma development in the large intestine, unless the clinical benefit justifies the potential risk to the patient.

### **Animal Toxicology**

Increased heart weights were evident in mice ( $\geq 2$  mg/kg/day after 3 months), rats ( $\geq 0.3$  mg/kg/day after 2 years) and dogs ( $\geq 0.5$  mg/kg/day after 12 months) following treatment with rosiglitazone (approximately 3, 2 and 0.3 times human AUC at the maximum recommended human daily dose, respectively). Morphometric analysis of the hearts indicated ventricular hypertrophy, which is considered to be due to increased workload as a result of plasma volume expansion.

Two ongoing echocardiography studies in patients with type 2 diabetes (given 4mg AVANDIA twice daily for 52 weeks [n=86] or 8mg AVANDIA once daily for 26 weeks [n=90]), have shown no deleterious alteration in cardiac structure or function. These studies were designed to detect a change in left ventricular mass of 10% or more.

### **Use in Pregnancy (Category B3)**

Rosiglitazone was not teratogenic when given to pregnant rats or rabbits during the period of organogenesis, at doses associated with respective exposures up to about 20 and 70 times those anticipated clinically (based on AUC). Following oral administration, rosiglitazone and/or its metabolites crossed the placenta and caused foetal death and retardation of foetal development in rats and rabbits, with no-effect doses of approximately 4 times anticipated clinical exposure (based on AUC) in both species. There was no effect on the embryo when rosiglitazone was given to rats prior to, or during implantation or early organogenesis.

Rosiglitazone has been reported to cross the human placenta and to be detectable in foetal tissues. There are no adequate data and well-controlled studies in pregnant women. Therefore, AVANDIA should not be used during pregnancy unless the expected therapeutic benefit outweighs the potential risk to the foetus.

Current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, neonatal morbidity and mortality. The use of insulin is generally recommended for patients with Type 2 diabetes during pregnancy, to maintain blood glucose levels as close to normal as possible.

### **Use in Lactation**

Following oral administration of radiolabelled rosiglitazone to lactating rats, the parent drug and/or its metabolites were secreted into the milk. It is not known whether rosiglitazone is secreted into human milk. Treatment of rats in pregnancy through lactation with rosiglitazone decreased postnatal survival, growth and development of the offspring, with a maternal no-effect dose level associated with a plasma AUC of about 3 times the maximum anticipated human value. Therefore, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### **Use in Children**

There are no data available on the use of AVANDIA in patients under 18 years of age, and therefore its use in this age group is not recommended.

### **Interactions**

Co-administration of rosiglitazone with gemfibrozil (an inhibitor of CYP 2C8) resulted in increased rosiglitazone plasma concentrations (see **Pharmacokinetics**). Since there is a potential for an increase in the risk of dose-related adverse events, a decrease in rosiglitazone dose may be needed.

Co-administration of rosiglitazone and rifampicin (an inducer of CYP 2C8) resulted in decreased rosiglitazone plasma concentrations (see **Pharmacokinetics**). Therefore, close monitoring of glycaemic control and changes in diabetic treatment should be considered.

Concomitant administration with other oral antidiabetic agents including metformin, glibenclamide and acarbose did not result in any clinically significant pharmacokinetic or pharmacodynamic interactions with AVANDIA.

AVANDIA had no effects on the steady state pharmacokinetics of digoxin or warfarin nor did it affect the anti-coagulant activity of warfarin.

Pre-treatment with ranitidine did not alter the pharmacokinetics of single oral or intravenous doses of rosiglitazone, suggesting that absorption of oral rosiglitazone is not altered by increases in gastrointestinal pH.

*In vitro* studies demonstrate that AVANDIA is predominantly metabolised by CYP 2C8, with CYP 2C9 contributing as only a minor pathway. Since there are no known inhibitors of CYP2C8 used clinically, concomitant drug therapy is not expected to inhibit rosiglitazone clearance. In addition, AVANDIA had no clinically relevant effect on the pharmacokinetics of S(-)-warfarin, a substrate for CYP 2C9.

Rosiglitazone caused a moderate inhibition of CYP2C8 and a minor inhibition of CYP2C9 *in vitro*. Significant inhibition of these enzymes is unlikely to occur at therapeutic doses (see **Pharmacokinetics**). Since there are only a few known substrates for CYP2C8 (paclitaxel, cerivastatin), the potential for an interaction involving this enzyme is even more unlikely.

No clinically relevant effects on nifedipine or oral contraceptives (components ethinyloestradiol and norethindrone) were observed after co-administration with AVANDIA confirming a low probability of clinically relevant interactions with drugs metabolised by CYP 3A4.

Moderate ingestion of alcohol with AVANDIA has no effect on glycaemic control.

#### **Driving or operating machinery**

There have been no studies to investigate the effect of AVANDIA on driving performance or the ability to operate machinery. The clinical status of the patient and the adverse event profile of AVANDIA should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

## **ADVERSE EVENTS**

In clinical trials, adverse experiences with AVANDIA were mostly mild to moderate in nature. In placebo-controlled studies, AVANDIA was well-tolerated when used as monotherapy or in combination with SUs and metformin. The need for discontinuation of therapy due to adverse experience occurred in 7.5% of patients treated with AVANDIA compared with 8.2% of placebo patients (in placebo controlled studies).

**Table 6: Most commonly reported adverse experiences (≥5% in any treatment group) in double blind monotherapy studies**

Preferred Term	AVANDIA	Placebo	Metformin	Sulfonylureas*
	monotherapy			
	N = 2526	N = 601	N = 225	N = 626
	n (%)	n (%)	n (%)	n (%)
Patients with Aes	1742 (69.0%)	374 (62.2%)	172 (76.4%)	438 (70.0%)
Upper respiratory tract infection	251 (9.9%)	52 (8.7%)	20 (8.9%)	46 (7.3%)
Injury	192 (7.6%)	26 (4.3%)	17 (7.6%)	38 (6.1%)
Headache	148 (5.9%)	30 (5.0%)	20 (8.9%)	34 (5.4%)

Back pain	102 (4.0%)	23 (3.8%)	9 (4.0%)	31 (5.0%)
Hyperglycaemia	99 (3.9%)	34 (5.7%)	10 (4.4%)	51 (8.1%)
Fatigue	92 (3.6%)	30 (5.0%)	9 (4.0%)	12 (1.9%)
Sinusitis	82 (3.2%)	27 (4.5%)	12 (5.3%)	16 (3.0%)
Diarrhoea	59 (2.3%)	20 (3.3%)	35 (15.6%)	19 (3.0%)
Hypoglycaemia	16 (0.6%)	1 (0.2%)	3 (1.3%)	37 (5.9%)

\* Includes patients receiving glibenclamide (N=514), gliclazide (N=91) or glipizide (N=21).

### **Cardiac Disorders**

An increased incidence of heart failure has been observed when rosiglitazone (at both 4 mg and 8 mg) was added to treatment regimens that include sulfonylurea or insulin. 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 (see **Precautions**). There were too few events to confirm a dose relationship: however, the incidence of heart failure was generally higher with 8 mg rosiglitazone compared to 4 mg rosiglitazone (total daily dose).

In a retrospective analysis of data from pooled clinical studies, the overall incidence of events typically associated with myocardial ischaemia was higher for rosiglitazone containing regimens, 2.00% versus comparators, 1.53% [Hazard ratio 1.30 (95% confidence interval 1.004 – 1.69)]. A small number of events typically associated with myocardial ischaemia were observed when rosiglitazone was added to established insulin therapy and these occurred at a higher frequency with the combination (2.77%) compared with insulin alone (1.36%) (see **Precautions**).

In ADOPT, a 4 to 6 year study of glycaemic control with monotherapy in recently diagnosed patients with T2DM, there was a similar risk of cardiovascular events for subjects given rosiglitazone, glibenclamide and metformin: the 60 month cumulative incidence per 100 patient-years (95% CI) was 0.18 (0.16 to 0.21) for rosiglitazone, 0.18 (0.15 to 0.20) for glibenclamide and 0.22 (0.20 to 0.25) for metformin. Incidence rates were also similar for myocardial ischaemia: 0.10 (0.08 to 0.12) for rosiglitazone, 0.08 (0.06 to 0.10) for glibenclamide and 0.11 (0.09 to 0.13) for metformin. Using an alternative definition for myocardial ischaemia on adjudicated events, there was no statistically significant difference between the three groups.

### **Oedema**

Oedema was reported in 4.8% of patients taking AVANDIA, compared to 1.3% on placebo, 1.0% on sulfonylureas and 2.2% on metformin. Treatment was required for 1.2% of patients with an adverse event of oedema. These adverse experiences infrequently led to withdrawal. Oedema was generally dose-related and was more frequently observed when rosiglitazone was used in combination with a sulfonylurea or insulin.

### **Metabolism and Nutrition Disorders**

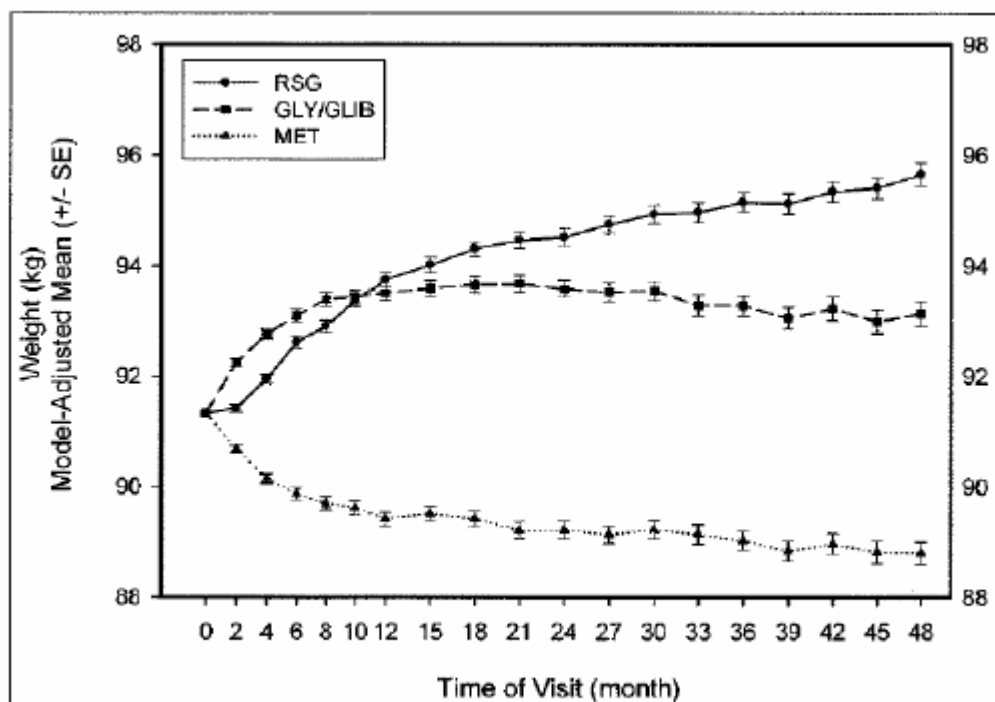
Hypercholesterolaemia was reported in 3.4% of patients. The elevated total cholesterol levels were associated with an increase in both LDLc (n=2048) and HDLc (n=2177) and the ratio of total cholesterol:HDLc was unchanged or decreased in long term studies (n=886 after 12 months' therapy). Overall, these experiences were generally mild to moderate and usually did not require discontinuation of treatment.

An increase in weight was reported as an adverse experience by 0.9% of patients on AVANDIA.

Dose-related weight gain was seen with AVANDIA alone and in combination with other hypoglycaemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation (see **Clinical Trials**).

In ADOPT, a 4 to 6 year study of glycaemic control with monotherapy in recently diagnosed patients with T2DM, there was a significant increase in body weight for patients given rosiglitazone, adjusted mean difference (95% CI) 2.5 (2.0 to 3.1) kg compared with glibenclamide, and 6.9 (6.3 to 7.4) kg compared to metformin. This weight change with AVANDIA occurred consistently over the duration of the study, compared with weight loss with metformin, as shown below:

**Figure 4 Weight gain in the ADOPT study**



Data Source: Table 8.6.5 and Table 8.6.6.

Similar increases in waist and hip circumference were seen. There was a significant difference in the change from baseline in waist circumference, with net gain for rosiglitazone, compared with metformin, adjusted mean difference (95% CI) 41.3 (31.9 to 50.6) mm. There was also a significant difference in the change from baseline in hip circumference, with net gain for rosiglitazone, compared with glibenclamide, adjusted mean difference (95% CI) 25.0 (15.4 to 34.6) mm, and metformin, 52.9 (43.8 to 62.0) mm.

In keeping with its mechanism of action, AVANDIA given as monotherapy is not associated with hypoglycaemia. In clinical trials, AVANDIA did not potentiate the hypoglycaemic effects of sulfonylureas. However, patients receiving rosiglitazone in combination with insulin or oral hypoglycaemic agents may be at risk for hypoglycaemia and a reduction in the dose of the concomitant agent may be necessary.

**Blood Disorders**

Across all controlled clinical studies, decreases in haemoglobin and haematocrit (mean decreases in individual studies  $\leq 1.0$  g/dL and  $\leq 3.3\%$ , respectively) were observed for both AVANDIA alone and in combination with metformin or sulfonylurea. The changes occurred primarily during the first

4 to 8 weeks of therapy and remained relatively constant thereafter. Anaemia (decreased haemoglobin) was reported at an incidence of 1.9% in double-blind studies with AVANDIA. The incidence of anaemia was higher when AVANDIA was used in combination with metformin (7.1%). Lower pre-treatment haemoglobin/haematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anaemia in these studies.

White blood cell counts also decreased slightly in patients treated with AVANDIA. The observed changes may be related to the increased plasma volume observed with treatment with AVANDIA and have not been associated with any significant haematologic clinical effects.

### ***Hepatobiliary Disorders***

In a large clinical program (4327 patients treated with AVANDIA) the incidence of elevations of ALT greater than three times the upper limit of normal was equal to placebo (0.2%) and less than that of the active comparators (0.5% metformin /SUs). The incidence of reports of all adverse experiences relating to liver and biliary systems also was low and equal to placebo (0.7%).

### ***Musculoskeletal, connective tissue and bone disorders***

Bone fractures were commonly seen in rosiglitazone monotherapy vs. metformin or glibenclamide monotherapy. The majority of the fractures in the females who received rosiglitazone were reported in the upper arm, hand and foot (see **Precautions**).

### **Post Marketing Adverse Events**

Rare and very rare events were determined from post-marketing data and refer to reporting rate rather than true frequency.

Post-marketing reports of congestive heart failure and pulmonary oedema have been received rarely.

Post-marketing reports of hepatic dysfunction, primarily evidenced by elevated hepatic enzymes, have been received rarely. In very rare cases a fatal outcome has been reported. A causal relationship to rosiglitazone has not been established.

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

Very rare post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with rosiglitazone (see **Precautions**).

## **DOSAGE AND ADMINISTRATION**

AVANDIA therapy can be initiated at 4mg/day. This dose can be increased to 8mg/day after 6-8 weeks if greater glycaemic control is required. AVANDIA may be given once or twice a day (see **Clinical Trials**).

AVANDIA may be taken with or without food.

No dose adjustment is required in the elderly.

Rosiglitazone dose adjustment may be needed when rosiglitazone is co-administered with certain other drugs (see **Interactions, Pharmacokinetics**).

No dose adjustment is required in patients with varying degrees of renal insufficiency, including patients with end stage renal disease on chronic haemodialysis.

No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh A). Owing to a difference in pharmacokinetics and limited experience, AVANDIA is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B/C). Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased transaminase levels (ALT > 2.5x upper limit of normal) at the start of treatment (see **Precautions**).

#### **Combination with sulfonylurea**

In patients administered rosiglitazone in combination with a sulfonylurea, the dose of rosiglitazone can be initiated at 4 mg/day and if further glycaemic control is required then the dose should only be increased cautiously to 8 mg/day following an appropriate clinical evaluation to assess the patient's risk of developing adverse events relating to fluid retention (see **Precautions** and **Adverse Events**).

### **OVERDOSAGE**

Limited data are available with regard to overdosage in humans. In clinical studies in volunteers AVANDIA has been administered at single oral doses of up to 20mg and was well tolerated. In the event of an overdose, it is recommended that appropriate supportive treatment should be initiated as dictated by the patient's clinical status. AVANDIA is highly protein bound and is not cleared by haemodialysis.

### **STORAGE**

Store below 30°C. Shelf life at this temperature is 2 years.

### **PRESENTATION**

Film coated, pentagonal shaped Tiltab<sup>®</sup> tablets. The tablet strengths are distinguished by colour: 4.0 mg (orange) and 8.0 mg (red-brown).

Each tablet strength is provided in opaque blister packs (PVC / aluminium) in the following pack sizes:

4mg : 7, 28 tablets

8mg : 28 tablets

### **NAME AND ADDRESS OF THE SPONSOR**

GlaxoSmithKline Australia Pty Ltd  
1061 Mountain Highway  
Boronia Victoria 3155  
Australia  
Telephone: (03) 9721 6000

Date of TGA Approval: 14 August 2008

Date of most recent amendment: 14 October 2008

Issue No. 17 (M)