AVANDAMET® PRODUCT INFORMATION
(rosiglitazone & metformin hydrochloride)
1/500, 2/500, 4/500, 2/1000 & 4/1000

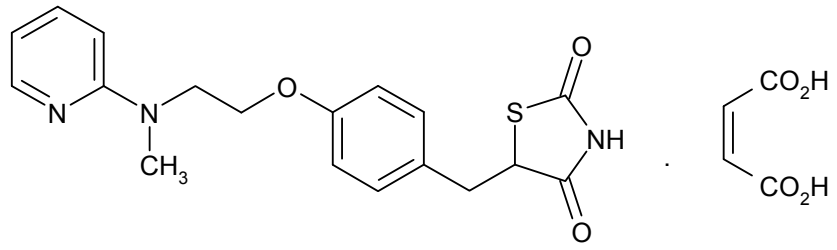
Life-threatening lactic acidosis can occur due to accumulation of metformin. Risk factors include renal impairment, old age and the use of high doses of metformin above 2000 mg per day.

The use of AVANDAMET is not recommended in patients with known ischaemic heart disease, particularly those taking nitrates. Rosiglitazone 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 MEDICINE

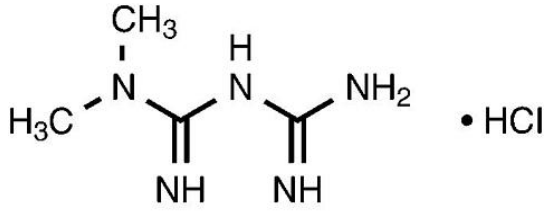
AVANDAMET (rosiglitazone maleate and metformin hydrochloride) contains two oral antihyperglycaemic drugs used in the management of type 2 diabetes, rosiglitazone maleate and metformin hydrochloride. Rosiglitazone maleate is chemically designated as (±)-5-[[4-[2-(methyl-2-pyridinylamino) ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (*Z*)-2-butenedioate (1:1).

The structural formula is:



Molecular weight: 473.52 (357.44 free base)
CAS number : 0155141-29-0

Metformin hydrochloride (1,1-dimethylbiguanide hydrochloride) has a molecular formula of $C_4H_{11}N_5 \bullet HCl$. The structural formula is as shown below:



Molecular weight: 165.63 (129.16 free base)
CAS number : 1115-70-4

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.

Metformin hydrochloride is a white to off-white crystalline compound which is freely soluble in water, slightly soluble in ethanol (98%) and is practically insoluble in acetone, ether and chloroform.

AVANDAMET tablets also contain hypromellose, lactose, magnesium stearate, microcrystalline cellulose, macrogol 400, povidone, sodium starch glycolate, titanium dioxide and one or both of the following: iron oxide red and iron oxide yellow .

PHARMACOLOGY

Pharmacodynamics

AVANDAMET combines two antihyperglycaemic agents with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes, rosiglitazone maleate, a member of the thiazolidinedione class and metformin hydrochloride, a member of the biguanide class. Thiazolidinediones act primarily by reducing insulin resistance and biguanides act primarily by decreasing endogenous hepatic glucose production.
The pharmacological properties of each component are detailed below.

Rosiglitazone:

Rosiglitazone is a selective and potent agonist at the PPARγ (peroxisomal proliferator activated gamma) nuclear receptor and is a member of the thiazolidinedione class of antihyperglycaemic agents.

Rosiglitazone 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, rosiglitazone improves metabolic control by lowering blood glucose, circulating insulin and free fatty acids.

The antihyperglycaemic activity of rosiglitazone has been demonstrated in a number of rodent models of type 2 diabetes. In addition, rosiglitazone preserved ß-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. Rosiglitazone has also been shown to significantly delay the onset of renal dysfunction and systolic hypertension. Rosiglitazone did not stimulate pancreatic insulin secretion or induce hypoglycaemia in rats and mice.

Metformin:

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:

- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Pharmacokinetics

Absorption:
AVANDAMET:
In a bioequivalence and dose proportionality study of AVANDAMET 4 mg/500 mg, both the rosiglitazone component and the metformin component were bioequivalent to co-administered 4 mg rosiglitazone maleate tablet and 500 mg metformin hydrochloride tablet under fasted condition. In this study, dose proportionality of rosiglitazone in the combination formulations of 1 mg/500 mg and 4 mg/500 mg was demonstrated.

A further bioequivalence and dose proportionality study demonstrated that the AVANDAMET combination formulation 4 mg/1000 mg was bioequivalent to two tablets of AVANDAMET 2 mg/500 mg. In addition, this study also established dose proportionality of rosiglitazone between the two combination tablet strengths of AVANDAMET 2 mg/1000 mg and 4 mg/1000 mg.

Administration of AVANDAMET 4mg/500mg with food resulted in no change in overall exposure (AUC) for either rosiglitazone or metformin. However, there were decreases in Cmax of both components (22% for rosiglitazone and 15% for metformin, respectively) and a delay in Tmax of both components (1.5 hrs for rosiglitazone and 0.5 hrs for metformin, respectively. These changes are not likely to be clinically significant. The pharmacokinetics of both the rosiglitazone component and the metformin component of AVANDAMET when taken with food were similar to the pharmacokinetics of rosiglitazone and metformin when administered concomitantly as separate tablets with food.

Rosiglitazone maleate:
Rosiglitazone is rapidly and completely absorbed after oral administration, with negligible first pass metabolism. Absolute bioavailability of rosiglitazone following both a 4 and an 8 mg oral dose is approximately 99%. Plasma concentrations of rosiglitazone peak at around 1 hour after dosing and are approximately dose proportional over the therapeutic dose range. Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), although a small decrease in Cmax (approximately 20-28%) and a delay in Tmax (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 rosiglitazone at any particular time in relation to meals. The absorption of rosiglitazone is not affected by increases in gastric pH.

Metformin hydrochloride:
After oral administration, metformin hydrochloride is absorbed along the entire gastrointestinal mucosa. Studies using single oral doses of metformin tablets indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an increase in elimination. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations are reached in24-48 hours and are generally less than 1 μg/mL. During controlled clinical trials, maximum metformin plasma levels did not generally exceed 5 μg/mL, even at maximum doses.

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

Metformin hydrochloride:
Metformin is not bound to plasma proteins.

Metabolism:
Rosiglitazone maleate:.

Metabolism of rosiglitazone 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 rosiglitazone are not considered to have any clinical relevance.

In vitro data demonstrate that rosiglitazone 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 rosiglitazone, therefore there is a low probability of significant metabolism-based interactions with drugs metabolised by these P450 enzymes (see **Interactions with Other Medicines**).

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 **Interactions with Other Medicines**).

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 **Interactions with Other Medicines**).

Metformin hydrochloride:
Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism.

Excretion:
Rosiglitazone maleate:
The terminal elimination half-life of rosiglitazone 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 rosiglitazone between males and females, or between elderly and non-elderly patients.

In patients with moderate to severe (Child-Pugh B/C) hepatic disease, unbound Cmax 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 rosiglitazone.

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

Metformin hydrochloride:
In patients with decreased renal function (based on measured creatinine clearance), the plasma half-life of metformin is prolonged and renal clearance is decreased in proportion to the decrease in creatinine clearance, e.g. if creatinine clearance is 10-30 mL/min, renal clearance is reduced to 20% of normal.

Special Populations:
AVANDAMET
Children: There are no data available on the use of AVANDAMET in children. Use of AVANDAMET in this age group is not recommended.

Rosiglitazone maleate:
Gender: In the pooled population pharmacokinetic analysis, there were no marked differences in the pharmacokinetics of rosiglitazone between males and females.

Elderly: In the pooled population pharmacokinetic analysis, age was not found to influence the pharmacokinetics of rosiglitazone to any significant extent.

Hepatic impairment: In patients with moderate to severe (Child-Pugh B/C) hepatic disease, unbound C_{max} 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 rosiglitazone.

Renal insufficiency: There are no clinically significant differences in the pharmacokinetics of rosiglitazone in patients with renal impairment or end stage renal disease on chronic dialysis.

CLINICAL TRIALS

There have been no clinical efficacy trials conducted with AVANDAMET tablets. However, studies utilizing the separate components have established the effective and safe use, and the additive benefit of the combination has been shown in patients with diabetes mellitus inadequately controlled despite maximal metformin therapy alone.

Bioequivalence of the AVANDAMET 4mg/1000mg tablets and an equivalent dose made up with the AVANDAMET 2mg/500mg tablets was demonstrated. Bioequivalence of AVANDAMET with coadministered rosiglitazone maleate tablets and metformin hydrochloride tablets was demonstrated (see **Pharmacokinetics**).

Rosiglitazone (monotherapy):
A total of 2,526 patients were treated with rosiglitazone 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.

In all these studies, long term and sustained improvements in glycaemic control (FPG and HbA1c) were demonstrated in type 2 diabetes with rosiglitazone given once or twice daily as monotherapy.

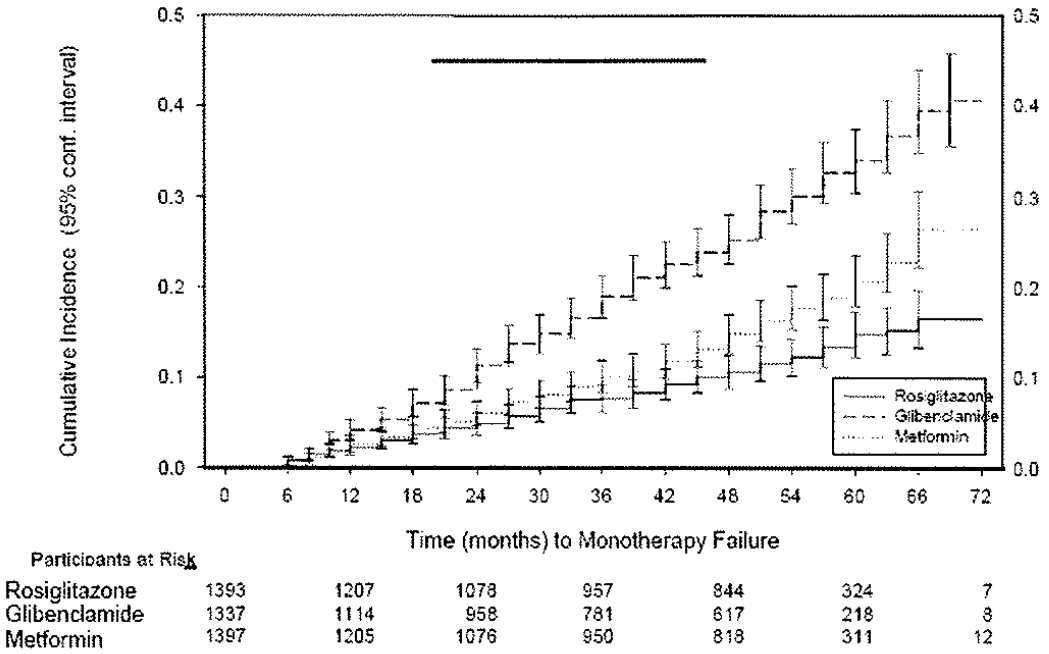
ADOPT (Study Protocol BRL-049653-048) was a randomised, double-blind, parallel group, active comparator controlled efficacy and safety trial of 4 to 6 years duration (median 4 years). The study was conducted in 473 centres (of which 467 enrolled at least one subject) in 17 countries in North America 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 ≤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 (≤1 month) insulin use to maintain glycaemic control for hospitalization or medical procedure/intervention; ≤2 weeks of oral hypoglycaemic agent (OHA) ≥2 weeks prior to screening or >2 weeks – 1 month OHA ≥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 1 Time to Monotherapy Failure



Participants at Risk

Rosiglitazone	1393	1207	1078	957	844	324	7
Glibenclamide	1337	1114	958	781	617	218	8
Metformin	1397	1205	1076	950	818	311	12

As shown above, rosiglitazone showed a significantly longer time to monotherapy failure compared with metformin and glibenclamide. 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 Effects**, Metabolic and Nutritional), fractures in women (especially of the lower limb), oedema and lipid effects.

Table 1: On-Therapy AEs Reported in ADOPT by ≥2.0%/100 Patient Years in Any Treatment Group

	Number of Subjects, n %					
	RSG N=1456 PY=4953.8		GLY/GLIB N=1441 PY=4243.6		MET N=1454 PY=4905.6	
Preferred Term	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY
Subjects who experienced at least one On-Therapy AE	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	189 (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
Hypercholestrolemia	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 2: 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

Rosiglitazone combination therapy with Metformin
Efficacy and safety data relevant to AVANDAMET come from three double-blind studies of rosiglitazone in combination with metformin (093, 094 and 044).

These studies recruited type 2 diabetic patients that were inadequately controlled on metformin alone (i.e. monotherapy failures). In studies 094 and 044, patients were randomised to receive either 4 mg/day, 8 mg/day rosiglitazone or placebo in addition to 2.5 g/day metformin. In study 094, rosiglitazone was administered once daily whereas in study

044, it was given bd (2 x 2 mg and 2 x 4 mg). In Study 093 patients received either 4 mg bd of rosiglitazone or placebo added on a daily dose of 2.5 g metformin. The primary end points in all studies were HbA1c levels and fasting plasma glucose (FPG) levels. All 3 studies ran for 26 weeks, with a 36 month open label extension of both 093 and 094, reported as study 113.

Improvements in metabolic control observed in these studies when rosiglitazone was used in combination with 2.5 g/day metformin are displayed in Table 3 below.

Table 3: Improvement in metabolic control in patients receiving rosiglitazone plus metformin (Studies 093, 094, 044)

Study	**094**		**093**	**044**	
	Rosiglitazone **4mg od + metformin* N=116**	Rosiglitazone **8mg od + metformin* N=110**	Rosiglitazone **4mg bd + metformin* N=103**	Rosiglitazone **2mg bd + metformin* N=48**	Rosiglitazone **4mg bd + metformin* N=47**
Change in HbA1c versus metformin alone	-1.0%	-1.2%	-0.8%	-1.0%	-1.4%
95% CI	-1.32, -0.63	-1.53, -0.83	-1.2, -0.5	-1.6, -0.3	-2.0, -0.7
p-value‡	<0.0001	<0.0001	<0.0001	0.0013	<0.0001
Change in FPG versus metformin alone	-2.2 mmol/L	-2.9 mmol/L	-3.1 mmol/L	-2.6 mmol/L	-3.3 mmol/L
95% CI	-2.9, -1.5	-3.7, -2.2	-3.9, -2.3	-3.9, -1.2	-4.8, -2.0
p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

* Metformin 2.5g/day

‡ For 094 significance level is 0.027; for 093 significance level is 0.05, for 044, significance level is 0.027

Rosiglitazone consistently and clinically significantly reduces HbA1c and FPG when used in combination with metformin. The two agents work through complementary mechanisms, apparently leading to a synergistic effect on glycaemic control.

An open-label extension (OLE) study (113) recruited patients from 093 and 094 and ran for a period of up to 3 years. This OLE study was primarily designed to evaluate the long term safety of rosiglitazone and metformin. However, for those patents who completed the study, the reduction in HbA1c achieved during the double blind phase was sustained over a period of 30 months.

INDICATIONS

AVANDAMET is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus (non-insulin dependent diabetes mellitus), as dual combination therapy in patients who are already treated with rosiglitazone and metformin in combination, or who are inadequately treated on metformin or rosiglitazone alone.

CONTRAINDICATIONS

AVANDAMET is contraindicated in patients with, previous history of hypersensitivity to rosiglitazone, metformin or any of the listed excipients.

Due to the metformin component of AVANDAMET it is contraindicated in diabetic ketoacidosis or pre-coma and renal failure (creatinine clearance < 60 mL/min).

AVANDAMET is contraindicated in patients with, juvenile diabetes mellitus that is uncomplicated and well regulated on insulin; diabetes mellitus regulated by diet alone; acute

complications of diabetes mellitus such as metabolic acidosis, coma, infection, gangrene, or during or immediately following surgery where insulin is essential.

AVANDAMET should be temporarily withheld in patients undergoing radiological studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

Risk of lactic acidosis: Because of the danger of lactic acidosis, AVANDAMET should not be used in the presence of the following conditions: diminished renal function; cardiovascular disease (e.g. coronary insufficiency, myocardial infarction and hypertension); conditions that may be associated with tissue hypoxia (e.g. gangrene, circulatory shock, acute significant blood loss); pulmonary embolism; severe hepatic dysfunction; pancreatitis; excessive alcohol intake; concomitant use of diuretics.

Initiation of rosiglitazone combination regimens (like other thiazolidinediones combination regimens) is contraindicated in patients with NYHA Class III and IV heart failure (see **Precautions**).

Use of rosiglitazone combination regimens is contraindicated in patients:

- 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

AVANDAMET 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, AVANDAMET treatment in premenopausal anovulatory patients with insulin resistance (e.g. patients with polycystic ovary syndrome) may result in resumption of ovulation. These patients may be at risk of pregnancy.

Premenopausal women have received rosiglitazone 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 during treatment with rosiglitazone. If unexpected menstrual dysfunction occurs the benefits of continued therapy should be reviewed.

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. AVANDAMET should not be initiated in patients on insulin. Insulin should not be initiated in patients on AVANDAMET. These combinations are not approved.

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

Congestive Heart Failure

Rosiglitazone, like other thiazolidinediones can cause or exacerbate congestive heart failure (CHF) in some patients. After initiation of AVANDAMET, 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 AVANDAMET 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 – AVANDAMET is not indicated for use with insulin.

Use of AVANDAMET in patients with NYHA Class I to IV heart failure or a 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 AVANDAMET in patients experiencing an acute coronary event is contraindicated. Furthermore, AVANDAMET should be discontinued during the acute phase.

Myocardial Ischaemia
Rosiglitazone has been shown to be associated with an increased risk of myocardial ischaemia (angina, infarction) in pooled short-term clinical studies (see below). AVANDAMET 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), rosiglitazone 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 rosiglitazone was added to established insulin therapy (see **Adverse Effects**), 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 ischemic events with rosiglitazone 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 rosiglitazone 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 Effects**). 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 Effects, *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 recommended.

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 rosiglitazone.

Monitoring of liver function:
In clinical trials with rosiglitazone, encompassing 2492 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevations of ALT levels. In post-marketing experience with rosiglitazone 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 AVANDAMET undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with AVANDAMET in all patients. Therapy with AVANDAMET 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 AVANDAMET 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 rosiglitazone, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with rosiglitazone 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 AVANDAMET should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Lactic Acidosis:
Lactic acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation during treatment with AVANDAMET. When it occurs it is fatal in approximately 50 % of cases. Lactic acidosis is a medical emergency and must be treated in hospital immediately. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications.
The reported risk of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases per 1,000 patient years). The onset is often subtle and accompanied by non-specific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific abdominal distress. Lactic acidosis may also occur in association with a

number of pathophysiological conditions, including diabetes mellitus, and when there is significant tissue hypoperfusion and hypoxaemia. Lactic acidosis is characterised by acidosis (decreased blood pH), elevated lactate levels with increased lactate/pyruvate ratio and electrolyte disturbances with an increased anion gap.

When metformin is implicated as the cause of lactic acidosis, metformin plasma levels greater than 5 μg/mL are generally found. Underlying renal disease, or a deterioration in renal function, result in reduced clearance of metformin and drug accumulation and are therefore major risk factors in lactic acidosis. The risk of lactic acidosis may therefore be significantly decreased by regular monitoring of renal function in patients taking metformin and by the use of the minimum effective dose of metformin. In addition, metformin therapy should be temporarily stopped in the presence of any condition associated with hypoxaemia or dehydration, in patients suffering from serious infections or trauma (particularly if gastrointestinal disturbances are noted or acidosis is suspected) and in those undergoing surgery.

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. Other trials suggest that this risk may also apply to men, although the risk of fracture among women appears higher than that among men. The risk of fracture should be considered in the care of patients treated with rosiglitazone, and attention should be given to assessing and maintaining bone health according to current standards of care.

Small decreases in spine and hip bone mineral density in men and women taking rosiglitazone have been reported in several studies. A correlation between changes in bone mineral density and fractures has not been established.

Eye Disorder:
Very rare post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with thiazolidinediones. 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.

Iodinated contrast agent:
The intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure. Therefore, due to the metformin component, **AVANDAMET** should be discontinued prior to, or at the time of the test and not reinstituted until renal function has been confirmed as normal.

Patients with renal impairment:
Limited data are available in patients with severe renal insufficiency being treated with rosiglitazone. As metformin is excreted by the kidney, creatinine clearance levels should be determined before initiating treatment with AVANDAMET and regularly thereafter. AVANDAMET should not be used in patients with renal dysfunction (creatinine clearance < 60 mL/min).

Special caution should be exercised in patients likely to have renal impairment, e.g. the elderly, or in situations where renal function may become impaired, e.g. dehydration, severe infection, or shock.

Patients with Hepatic Impairment:

In patients with mild hepatic impairment (Child-Pugh A, scores of 6 or less) no dose adjustment of rosiglitazone is required. However, due to limited experience with both rosiglitazone and metformin, AVANDAMET is not recommended in patients with hepatic impairment. (see Lactic Acidosis in **Precautions** section).

Elderly:
As metformin is excreted via the kidney, the initial and maintenance dosing of AVANDAMET should be conservative in elderly patients due to the potential for decreased renal function in this population. Any dosage adjustment should be based on renal function, which should be monitored (see **Precautions**).

Children:
There are no data available on the use of AVANDAMET in children, and therefore use of AVANDAMET in this age group is not recommended.

Alcohol is known to potentiate the effect of metformin on lactic metabolism. Patients should therefore be warned against excessive alcohol intake, acute or chronic, while taking AVANDAMET.

Periodic assessment of renal, hepatic and cardiovascular function is recommended during prolonged periods of treatment with metformin.

Patients receiving continuous metformin therapy should have an annual estimation of vitamin B12 levels because of reports of decreased vitamin B12 absorption.

Carcinogenicity, mutagenicity and impairment of fertility:
No animal studies have been conducted with the combined products in AVANDAMET. The following data are based on findings in studies performed with the rosiglitazone or metformin individually.

Rosiglitazone:
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 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 over stimulation 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, AVANDAMET 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.

Metformin:
Long term carcinogenicity studies of metformin have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately two to three times the recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumourigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day.

No evidence of a mutagenic potential of metformin was found in the Ames test (*S.typhimurium*), gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes), or *in vivo* micronucleus test (mouse bone marrow).

Fertility of male or female rats was unaffected by metformin administration at doses up to 600mg/kg/day, or approximately twice the maximum recommended human dose of 2000mg/day on a body surface area basis.

Animal Toxicology:
No animal studies have been conducted with the combined products in AVANDAMET. The following data are findings in studies performed with rosiglitazone or metformin individually.

Increased heart weights were evident in mice (≥2 mg/kg/day after 3 months), rats (≥0.3 mg/kg/day after 2 years) and dogs (≥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 rosiglitazone 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 C)
No animal studies have been conducted with the combined products in **AVANDAMET.** The following data are findings in studies performed with rosiglitazone or metformin individually.

Rosiglitazone alone 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.

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about 2 times the maximum recommended human daily dose on body surface area basis. Determination of foetal concentrations demonstrated a partial placental barrier to metformin.

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 for either rosiglitazone or metformin. Therefore, AVANDAMET 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. Studies in lactating rats also show that metformin is excreted into the milk and reached levels comparable to those in plasma. 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.

It is not known whether rosiglitazone or metformin is secreted into human milk. Therefore, a decision should be made whether to discontinue nursing or to discontinue AVANDAMET, taking into account the importance of the drug to the mother.

INTERACTIONS WITH OTHER MEDICINES

There have been no formal interaction studies for AVANDAMET. The following statements reflect the information available on the individual components (rosiglitazone and metformin). Adjustment of the rosiglitazone or metformin component doses may be needed when rosiglitazone-metformin is co-administered with certain other drugs (see **Precautions**, **Pharmacokinetics**).

Co-administration of rosiglitazone with gemfibrozil (an inhibitor of CYP2C8) 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 CYP2C8) 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 rosiglitazone.
Rosiglitazone 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 rosiglitazone is predominantly metabolised by CYP2C8, with CYP2C9 as only a minor pathway. In addition, clinical data have shown that

rosiglitazone had no clinically relevant effect on the pharmacokinetics of S(-)-warfarin (a substrate for CYP2C9).

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 section). 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 norethisterone) were observed after co-administration with rosiglitazone confirming a low probability of interaction with drugs metabolised by CYP3A4.

There is an increased risk of lactic acidosis in acute alcohol intoxication due to the metformin component of AVANDAMET (see **Precautions**).

Iodinated contrast media: Metformin should be temporarily withheld in patients undergoing radiological studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

Driving or operating machinery
No effects on the ability to drive or operate machinery have been observed with rosiglitazone or metformin.

ADVERSE EFFECTS

There have been no clinical efficacy trials conducted with AVANDAMET tablets however bioequivalence of AVANDAMET with co-administered rosiglitazone and metformin has been demonstrated. The data presented here relates to the co-administration of rosiglitazone and metformin, where rosiglitazone has been added to metformin. There have been no studies of metformin added to rosiglitazone.

Rosiglitazone and metformin
Adverse experiences (>5%) in patients during double blind and OLE for rosiglitazone in combination with metformin are presented in the table below.

Table 4 Most commonly reported adverse experiences (≥5% in any treatment group) in studies of Rosiglitazone in Combination with Metformin (Studies 093, 094, 044, 113)

Preferred term	RSG + MET (DB +OLE) (N = 651)		RSG + MET (DB) (N = 439)		MET (DB) (N = 276)	
	n	%	n	%	n	%
Patients with AEs	570	(87.6%)	350	(79.7%)	209	(75.7%)
Oedema dependent	49	(7.5%)	12	(2.7%)	1	(0.4%)
Fatigue	56	(8.6%)	21	(4.8%)	9	(3.3%)
Injury	110	(16.9%)	30	(6.8%)	19	(6.9%)
Pain	59	(9.1%)	17	(3.9%)	9	(3.3%)
Hypertension aggravated	44	(6.8%)	6	(1.4%)	14	(5.1%)
Dizziness	37	(5.7%)	14	(3.2%)	9	(3.3%)
Headache	65	(10.0%)	30	(6.8%)	23	(8.3%)
Abdominal pain	33	(5.1%)	12	(2.7%)	8	(2.9%)
Diarrhoea	101	(15.5%)	52	(11.8%)	39	(14.1%)
Nausea	45	(6.9%)	18	(4.1%)	7	(2.5%)
Hypercholesterolaemia	45	(6.9%)	9	(2.1%)	3	(1.1%)
Hyperlipidemia	64	(9.8%)	11	(2.5%)	0	0
Arthralgia	69	(10.6%)	25	(5.7%)	7	(2.5%)
Arthritis	34	(5.2%)	9	(2.1%)	7	(2.5%)
Back pain	63	(9.7%)	18	(4.1%)	10	(3.6%)
Anaemia	109	(16.7%)	39	(8.9%)	7	(2.5%)
Infection viral	66	(10.1%)	19	(4.3%)	11	(4.0%)
Upper respiratory tract infection	184	(28.3%)	57	(13.0%)	21	(7.6%)
Bronchitis	51	(7.8%)	11	(2.5%)	6	(2.2%)
Coughing	43	(6.6%)	11	(2.5%)	8	(2.9%)
Pharyngitis	33	(5.1%)	9	(2.1%)	8	(2.9%)
Sinusitis	72	(11.1%)	22	(5.0%)	13	(4.7%)
Urinary tract infection	69	(10.6%)	22	(5.0%)	12	(4.3%)

Adverse reactions (with suspected/probable relationship to treatment reported as more than an isolated case) in patients receiving concomitantly administered rosiglitazone and metformin in excess of metformin alone in double-blind studies are listed below, by system organ class and absolute frequency. Frequencies are defined as: common ≥ 1/100, < 1/10; uncommon ≥ 1/1000, < 1/100.

Red Blood Cell
Common: anaemia.

Metabolism and Nutritional
Common: hypoglycaemia.
Uncommon: hyperlipidaemia, diabetes mellitus aggravated, hypercholesterolaemia, weight increase.

Gastrointestinal System
Common: flatulence, nausea, gastritis, abdominal pain, vomiting.
Uncommon: anorexia, constipation.

Body as a Whole General
Uncommon: oedema dependent.

The following statements reflect the information available on the adverse event profile of the individual components (rosiglitazone and metformin).

Rosiglitazone:
Adverse experiences with rosiglitazone (monotherapy) were generally not dose related, were mostly mild and transient in nature. In placebo-controlled studies, rosiglitazone was well-tolerated when used as monotherapy or in combination with sulfonylureas and metformin. The need for discontinuation of therapy due to adverse experience occurred in 7.5% of patients treated with rosiglitazone compared with 8.2% of placebo patients (in placebo controlled studies).

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

Preferred Term	Rosiglitazone monotherapy N = 2526 n (%)	Placebo N = 601 n (%)	Metformin N = 225 n (%)	Sulfonylureas* N = 626 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 4mg and 8mg) was added to treatment regimens that include sulfonylurea or insulin. Patients who experienced heart failure were on average older, had longer duration of diabetes, and were mostly on the higher 8 mg daily dose of rosiglitazone. 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 was 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 rosiglitazone, 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.

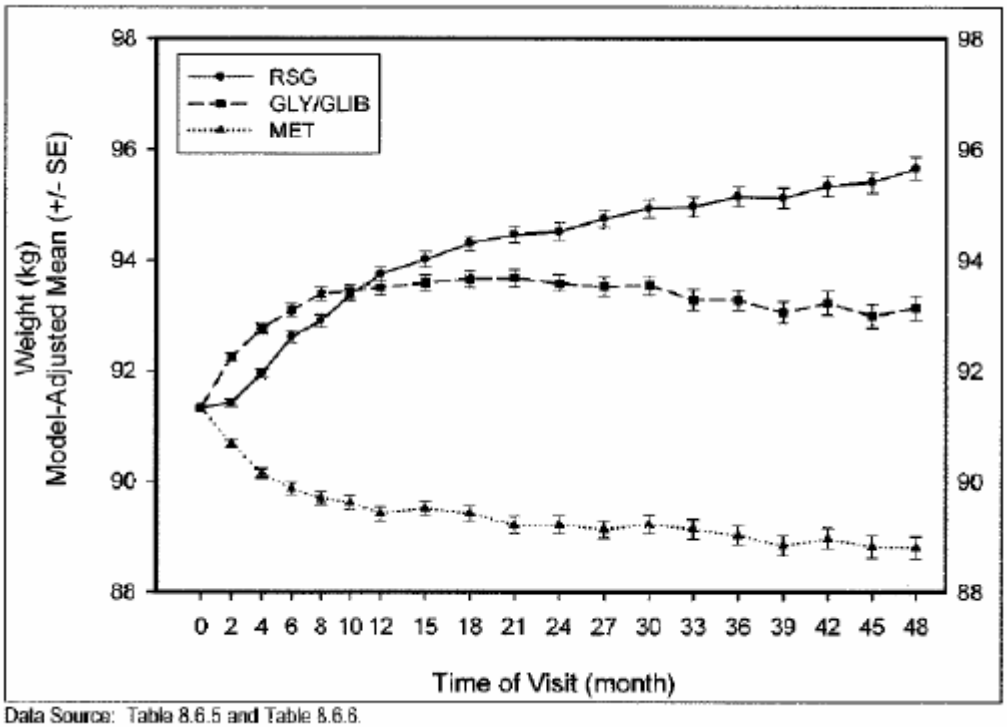
Metabolism and Nutrition Disorders

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 rosiglitazone.
Dose-related weight gain was seen with rosiglitazone 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 2 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, rosiglitazone given as monotherapy is not associated with hypoglycaemia. 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.

Other adverse reactions associated with rosiglitazone use are an increase in appetite and mild to moderate constipation.

Blood Disorders
Across all controlled clinical studies, decreases in haemoglobin and haematocrit (mean decreases in individual studies ≤1.0 g/dL and ≤3.3%, respectively) were observed for both rosiglitazone 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 rosiglitazone. The incidence of anaemia was higher when rosiglitazone 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 rosiglitazone. The observed changes may be related to the increased plasma volume observed with treatment with rosiglitazone and have not been associated with any significant haematologic clinical effects.

Hepatobiliary Disorders
In a large clinical program (4327 patients treated with rosiglitazone) 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 for rosiglitazone as monotherapy and in combination with other antidiabetic agents.

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 shock, angioedema, urticaria, rash and pruritis 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 thiazolidinediones (see **Precautions**).

Metformin hydrochloride:
Gastrointestinal:
Very common: Mild gastrointestinal symptoms (such as diarrhoea, nausea, vomiting, abdominal pain and loss of appetite) are the most frequent reactions to metformin (> 1/10), especially during the initial period. These symptoms are generally transient and resolve spontaneously during continued treatment.
Gastrointestinal side effects can possibly be avoided if metformin is taken with meals and if the dose is increased slowly. Occasionally, a temporary dose reduction can be considered.

Occurrence of gastrointestinal symptoms, once a patient is stabilised on any dose of metformin, could be due to lactic acidosis or other serious disease.

Common: Metallic taste

Very rare: Lactic acidosis (see **Precautions**) is very rare (< 1/10,000) but serious metabolic complication that can occur due to metformin accumulation during treatment.
The onset of lactic acidosis is often subtle and accompanied only by non-specific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarryhythmias with more marked acidosis. The patient and the patient's doctor must be aware of the possible importance of such symptoms and the patient should be instructed to notify the doctor immediately if they occur. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketomania).
Lactic acidosis is a medical emergency that must be treated in hospital. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures should be instituted promptly.

Dermatological:
Mild erythema has been reported in some hypersensitive individuals but the incidence is very rare (< 1/10,000).

Haematological:
A decrease of vitamin B_{12} absorption with a decrease in serum levels has been observed in patients treated long term with metformin and appears to be generally without clinical significance (< 1/10,000). Therefore serum B_{12} levels should be appropriately monitored and periodic parenteral B_{12} supplementation considered.

DOSAGE AND ADMINISTRATION

Life-threatening lactic acidosis can occur due to accumulation of metformin. Risk factors include renal impairment, old age and the use of high doses of metformin above 2000 mg per day.

Due to the metformin component, AVANDAMET should be given twice a day. Taking AVANDAMET with or just after food may reduce gastrointestinal symptoms associated with the metformin component.

The usual starting daily dose of AVANDAMET is 4 mg/1000 mg. The daily dose of rosiglitazone-metformin may be increased to maintain the individual's glycaemic control. Dose titration should be to a maximum recommended total daily dose of 8 mg rosiglitazone/2000 mg metformin.

Only one strength of AVANDAMET should be prescribed and used at any one time, and treatment with other metformin containing products should be discontinued. There is potential risk of accidental overdosing presented by the continuance of previously prescribed metformin containing products.

Dosage Recommendations
For patients inadequately controlled on metformin monotherapy: the usual starting dose of AVANDAMET is 4 mg rosiglitazone (total daily dose) plus the dose of metformin already being taken (see Table 6).

For patients inadequately controlled on rosiglitazone monotherapy: the usual starting dose of AVANDAMET is 1000 mg metformin (total daily dose) plus the dose of rosiglitazone already being taken (see Table 6).

When switching from combination therapy of rosiglitazone plus metformin as separate tablets: the usual starting dose of AVANDAMET is the dose of rosiglitazone and metformin already being taken (see Table 6).

Table 6: AVANDAMET Starting Dose

PRIOR THERAPY	Usual AVANDAMET Starting Dose	
Total daily dose	**Tablet strength**	**Number of tablets**
Metformin HCl*		
1000 mg/day	2 mg/500 mg	1 tablet bd
2000 mg/day	1 mg/500 mg	2 tablets bd
	2 mg/1000 mg	1 tablet bd
Rosiglitazone		
4 mg/day	2 mg/500 mg	1 tablet bd
8 mg/day	4 mg/500 mg	1 tablet bd

*For patients on doses of metformin HCl between 1000 and 2000 mg/day, initiation of AVANDAMET requires individualization of therapy.

The daily dose of AVANDAMET may then be increased according to the individual's glycaemic control:
- after an increase in metformin, dose titration is recommended if patients are not adequately controlled after 1-2 weeks
- after an increase in rosiglitazone, dose titration is recommended if patients are not adequately controlled after 6-8 weeks.

A slow increase of dose may reduce GI side effects (largely due to metformin); dose escalation should be by increments of 4mg/day rosiglitazone and/or 1000mg/day metformin, to a maximum recommended total daily dose of 8mg/2000mg.

The interval for dose adjustment should be individualised to patient's response. The full effect of dose adjustment may not be seen for six to eight weeks for the rosiglitazone component and one to two weeks for the metformin component.

Children:
There are no data available on the use of AVANDAMET in children, and therefore use of AVANDAMET in this age group is not recommended.

OVERDOSAGE

No data are available with regard to overdosage of AVANDAMET.

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

Large overdose of metformin or concomitant risks of lactic acidosis may lead to lactic acidosis which is a medical emergency and should be treated in hospital.

In the event of an overdose, it is recommended that appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The most effective method to remove lactate and metformin is haemodialysis, however rosiglitazone is highly protein bound and is not cleared by haemodialysis.

PRESENTATION AND STORAGE CONDITIONS

Film-coated oval tablets, debossed with gsk on one side, and the following debossing on the reverse side. The tablets are also distinguished by colour
1mg/500mg – 1/500 (yellow)
2mg/500mg – 2/500 (pale pink)
4mg/500mg – 4/500 (orange)
2mg/1000mg – 2/1000 (yellow)
4mg/1000mg – 4/1000 (pink)

Each tablet strength is presented in blister packs in the following pack sizes:
1mg/500mg: 14, 28, 56, 112 tablets
2mg/500 mg: 14, 28, 56, 112 tablets
4mg/500mg: 14, 28, 56, 112 tablets
2mg/1000mg: 14, 28, 56 tablets
4mg/1000mg: 14, 28, 56 tablets

Store below 30°C. Shelf life at this temperature is 3 years.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4, 436 Johnston Street,
Abbotsford, Victoria 3067
Australia

AVANDAMET is a trademark of the GlaxoSmithKline group of companies.

POISON SCHEDULE OF THE MEDICINE: S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 17 November 2004

DATE OF MOST RECENT AMENDMENT: 16 December 2014

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