ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 1 mg/500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg of rosiglitazone (as rosiglitazone maleate) and 500 mg of metformin hydrochloride (corresponding to metformin free base 390 mg).

Excipients:
Each tablet contains lactose (approximately 6 mg).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow film-coated tablets marked "gsk" on one side and "1/500" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AVANDAMET is indicated in the treatment of type 2 diabetes mellitus patients, particularly overweight patients:

- who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone.
- in triple oral therapy with sulphonylurea in patients with insufficient glycaemic control despite dual oral therapy with their maximally tolerated dose of metformin and a sulphonylurea (see section 4.4).

4.2 Posology and method of administration

The usual starting dose of AVANDAMET is 4 mg/day rosiglitazone plus 2000 mg/day metformin hydrochloride.

Rosiglitazone can be increased to 8 mg/day after 8 weeks if greater glycaemic control is required. The maximum recommended daily dose of AVANDAMET is 8 mg rosiglitazone plus 2000 mg metformin hydrochloride.

The total daily dose of AVANDAMET should be given in two divided doses.

Dose titration with rosiglitazone (added to the optimal dose of metformin) may be considered before the patient is switched to AVANDAMET.

When clinically appropriate, direct change from metformin monotherapy to AVANDAMET may be considered.

Taking AVANDAMET with or just after food may reduce gastrointestinal symptoms associated with metformin.

Triple oral therapy (rosiglitazone, metformin and sulphonylurea) (see section 4.4)

Medicinal product no longer authorised

- Patients on metformin and sulphonylurea: when appropriate AVANDAMET may be initiated at 4 mg/day rosiglitazone with the dose of metformin substituting that already being taken. An increase in the rosiglitazone component to 8 mg/day should be undertaken cautiously following appropriate clinical evaluation to assess the patient's risk of developing adverse reactions relating to fluid retention (see sections 4.4 and 4.8).
- Patients established on triple oral therapy: when appropriate, AVANDAMET may substitute rosiglitazone and metformin doses already being taken.

Where appropriate, AVANDAMET may be used to substitute concomitant rosiglitazone and metformin in existing dual or triple oral therapy to simplify treatment.

Elderly
As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking AVANDAMET should have their renal function monitored regularly (see sections 4.3 and 4.4).

Patients with renal impairment
AVANDAMET should not be used in patients with renal failure or renal dysfunction, e.g. serum creatinine levels > 135 µmol/l in males and > 110 µmol/l in females and/or creatinine clearance < 70 ml/min (see sections 4.3 and 4.4).

Children and adolescents
AVANDAMET is not recommended for use in children and adolescents below 18 years of age as there are no data available on its safety and efficacy in this age group (see sections 5.1 and 5.2).

4.3 Contraindications

AVANDAMET is contraindicated in patients with:

- hypersensitivity to rosiglitazone, to metformin hydrochloride or to any of the excipients
- cardiac failure or history of cardiac failure (New York Heart Association (NYHA) stages I to IV)
- an Acute Coronary Syndrome (unstable angina, NSTEMI and STEMI) (see section 4.4)
- acute or chronic disease which may cause tissue hypoxia such as:
    - cardiac or respiratory failure
    - recent myocardial infarction
    - shock
- hepatic impairment
- acute alcohol intoxication, alcoholism (see section 4.4)
- diabetic ketoacidosis or diabetic pre-coma
- renal failure or renal dysfunction e.g. serum creatinine levels > 135 µmol/l in males and > 110 µmol/l in females and/or creatinine clearance < 70 ml/min (see section 4.4)
- acute conditions with the potential to alter renal function such as:
    - dehydration
    - severe infection
    - shock
    - intravascular administration of iodinated contrast agents (see section 4.4)
    - lactation.

4.4 Special warnings and precautions for use

Lactic acidosis
Lactic acidosis is a very rare, but serious, metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis,

Medicinal product no longer authorised

prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia.

Diagnosis:
Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/l and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately (see section 4.9).

Renal function
As metformin is excreted by the kidney, serum creatinine concentrations should be determined regularly:
- at least once a year in patients with normal renal function
- at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly patients.

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with an NSAID.

Fluid retention and cardiac failure
Thiazolidinediones can cause fluid retention which may exacerbate or precipitate signs or symptoms of congestive heart failure. Rosiglitazone can cause dose-dependent fluid retention. The possible contribution of fluid retention to weight gain should be individually assessed as rapid and excessive weight gain has been reported very rarely as a sign of fluid retention. All patients, particularly those receiving concurrent insulin but also sulphonylurea therapy, those at risk for heart failure, and those with reduced cardiac reserve, should be monitored for signs and symptoms of adverse reactions relating to fluid retention, including weight gain and heart failure. AVANDAMET must be discontinued if any deterioration in cardiac status occurs.

The use of AVANDAMET in combination with a sulphonylurea or insulin may be associated with increased risks of fluid retention and heart failure (see section 4.8). The decision to initiate AVANDAMET in combination with a sulphonylurea should include consideration of alternative therapies. Increased monitoring of the patient is recommended if AVANDAMET is used in combination particularly with insulin but also with a sulphonylurea.

Heart failure was also reported more frequently in patients with a history of heart failure; oedema and heart failure was also reported more frequently in elderly patients and in patients with mild or moderate renal failure. Caution should be exercised in patients over 75 years because of the limited experience in this patient group. Since NSAIDs, insulin and rosiglitazone are all associated with fluid retention, concomitant administration may increase the risk of oedema.

Combination with insulin
An increased incidence of cardiac failure has been observed in clinical trials when rosiglitazone is 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. Insulin should only be added to established rosiglitazone therapy in exceptional cases and under close supervision.

Myocardial Ischaemia
A retrospective analysis of data from 42 pooled short-term clinical studies indicated that treatment with rosiglitazone may be associated with an increased risk of myocardial ischaemic events. However, in their entirety the available data on the risk of cardiac ischaemia are inconclusive (see section 4.8). There are limited clinical trial data in patients with ischaemic heart disease and/or peripheral arterial disease. Therefore, as a precaution, the use of rosiglitazone is not recommended in these patients, particularly those with myocardial ischaemic symptoms.

Medicinal product no longer authorised

Acute Coronary Syndrome (ACS)
Patients experiencing an ACS have not been studied in rosiglitazone controlled clinical trials. In view of the potential for development of heart failure in these patients, rosiglitazone should therefore not be initiated in patients having an acute coronary event and it should be discontinued during the acute phase (see section 4.3).

Monitoring of liver function
There have been rare reports of hepatocellular dysfunction during post-marketing experience with rosiglitazone (see section 4.8). There is limited experience with rosiglitazone in patients with elevated liver enzymes (ALT > 2.5 times the upper limit of normal). Therefore, liver enzymes should be checked prior to the initiation of therapy with AVANDAMET in all patients and periodically thereafter based on clinical judgement. Therapy with AVANDAMET should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 times the upper limit of normal) or with any other evidence of liver disease. If ALT levels are increased to > 3 times the upper limit of normal during AVANDAMET therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 times the upper limit of normal, therapy 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, therapy should be discontinued.

Eye disorders
Post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with thiazolidinediones, including rosiglitazone. Many of these patients reported concurrent peripheral oedema. It is unclear whether or not there is a direct association between rosiglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity and appropriate ophthalmologic referral should be considered.

Weight gain
In clinical trials with rosiglitazone there was evidence of dose-related weight gain, which was greater when used in combination with insulin. Therefore weight should be closely monitored, given that it may be attributable to fluid retention, which may be associated with cardiac failure.

Anaemia
Rosiglitazone treatment is associated with a dose-related reduction of haemoglobin levels. In patients with low haemoglobin levels before initiating therapy, there is an increased risk of anaemia during treatment with AVANDAMET.

Hypoglycaemia
Patients receiving AVANDAMET in combination with a sulphonylurea or insulin may be at risk for dose-related hypoglycaemia. Increased monitoring of the patient and a reduction in the dose of the concomitant agent may be necessary.

Surgery
As AVANDAMET contains metformin hydrochloride, the treatment should be discontinued 48 hours before elective surgery with general anaesthesia and should not usually be resumed earlier than 48 hours afterwards.

Administration of iodinated contrast agent
The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure. Therefore, due to the metformin active substance, AVANDAMET should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.5).

Bone disorders

Medicinal product no longer authorised

Long-term studies show an increased incidence of bone fractures in patients, particularly female patients, taking rosiglitazone (see section 4.8). The majority of the fractures have occurred in the upper limbs and distal lower limbs. In females, this increased incidence was noted after the first year of treatment and persisted during long-term treatment. The risk of fracture should be considered in the care of patients, especially female patients, treated with rosiglitazone.

Other precautions
Premenopausal women have received rosiglitazone during clinical studies. Although hormonal imbalance has been seen in preclinical studies (see section 5.3), no significant undesirable effects associated with menstrual disorders have been observed. As a consequence of improving insulin sensitivity, resumption of ovulation may occur in patients who are anovulatory due to insulin resistance. Patients should be aware of the risk of pregnancy (see section 4.6).

AVANDAMET should be used with caution during concomitant administration of CYP2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin), due to the effect on rosiglitazone pharmacokinetics (see section 4.5). Furthermore, AVANDAMET should be used with caution during concomitant administration of cationic medicinal products that are eliminated by renal tubular secretion (e.g. cimetidine) due to the effect on metformin pharmacokinetics (see section 4.5). Glycaemic control should be monitored closely. AVANDAMET dose adjustment within the recommended posology or changes in diabetic treatment should be considered.

All patients should continue their diet with regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
The usual laboratory tests for diabetes monitoring should be performed regularly.

AVANDAMET tablets contain lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for AVANDAMET, however the concomitant use of the active substances in patients in clinical studies and in widespread clinical use has not resulted in any unexpected interactions. The following statements reflect the information available on the individual active substances (rosiglitazone and metformin).

There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic insufficiency) due to the metformin active substance of AVANDAMET (see section 4.4). Avoid consumption of alcohol and medicinal products containing alcohol.

Cationic medicinal products that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and C_{max} by 81%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered (see section 4.4).

In vitro studies demonstrate that rosiglitazone is predominantly metabolised by CYP2C8, with CYP2C9 as only a minor pathway.

Co-administration of rosiglitazone with gemfibrozil (an inhibitor of CYP2C8) resulted in a twofold increase in rosiglitazone plasma concentrations. Since there is a potential for an increase in the risk of dose-related adverse reactions, a decrease in rosiglitazone dose may be needed. Close monitoring of glycaemic control should be considered (see section 4.4).

Medicinal product no longer authorised

Co-administration of rosiglitazone with rifampicin (an inducer of CYP2C8) resulted in a 66% decrease in rosiglitazone plasma concentrations. It cannot be excluded that other inducers (e.g. phenytoin, carbamazepine, phenobarbital, St John's wort) may also affect rosiglitazone exposure. The rosiglitazone dose may need to be increased. Close monitoring of glycaemic control should be considered (see section 4.4).

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

Concomitant administration of rosiglitazone with the oral antihyperglycaemic agents glibenclamide and acarbose did not result in any clinically relevant pharmacokinetic interactions.

No clinically relevant interactions with digoxin, the CYP2C9 substrate warfarin, the CYP3A4 substrates nifedipine, ethinylestradiol or norethindrone were observed after co-administration with rosiglitazone.

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.

Combination requiring precautions for use
Glucocorticoids (given by systemic and local routes) beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment. If necessary, the dosage of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.
ACE-inhibitors may decrease the blood glucose levels. If necessary, the dosage of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

4.6 Pregnancy and lactation

For AVANDAMET no preclinical or clinical data on exposed pregnancies or lactation are available.

Rosiglitazone has been reported to cross the human placenta and to be detectable in foetal tissues. There are no adequate data from the use of rosiglitazone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Therefore, AVANDAMET should not be used during pregnancy. If a patient wishes to become pregnant or if pregnancy occurs, treatment with AVANDAMET should be discontinued unless the expected benefit to the mother outweighs the potential risk to the foetus.

Both rosiglitazone and metformin have been detected in the milk of experimental animals. It is not known whether breast-feeding will lead to exposure of the infant to the medicinal product. AVANDAMET must therefore not be used in women who are breast-feeding (see section 4.3).

4.7 Effects on ability to drive and use machines

AVANDAMET has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are presented below for each of the component parts of AVANDAMET. An adverse reaction is only presented for the fixed dose combination if it has not been seen in one of the component parts of AVANDAMET or if it occurred at a higher frequency than that listed for a component part.

Medicinal product no longer authorised

Adverse reactions for each treatment regimen are presented below by system organ class and absolute frequency. For dose-related adverse reactions the frequency category reflects the higher dose of rosiglitazone. Frequency categories do not account for other factors including varying study duration, pre-existing conditions and baseline patient characteristics. Adverse reaction frequency categories assigned based on clinical trial experience may not reflect the frequency of adverse events occurring during normal clinical practice. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000 including isolated reports).

AVANDAMET

Data from double-blind studies confirm that the safety profile of concomitant rosiglitazone and metformin is similar to that of the combined adverse reaction profile for the two medicinal products. Data with AVANDAMET is also consistent with this combined adverse reaction profile.

Clinical trial data (addition of insulin to established AVANDAMET therapy)
In a single study (n=322) where insulin was added to patients established on AVANDAMET, no new adverse events were observed in excess of those already defined for either AVANDAMET or rosiglitazone combination therapies.
However, the risk of both fluid related adverse events and hypoglycaemia are increased when AVANDAMET is used in combination with insulin.

Rosiglitazone

Clinical trial data
Adverse reactions for each treatment regimen are presented below by system organ class and absolute frequency. For dose-related adverse reactions the frequency category reflects the higher dose of rosiglitazone. Frequency categories do not account for other factors including varying study duration, pre-existing conditions and baseline patient characteristics.

Table 1 lists adverse reactions identified from an overview of clinical trials involving over 5,000 rosiglitazone-treated patients. Within each system organ class, adverse reactions are presented in the table by decreasing frequency for the rosiglitazone monotherapy treatment regimen. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Medicinal product no longer authorised

Table 1. The frequency of adverse reactions identified from clinical trial data with rosiglitazone

Adverse reaction	Frequency of adverse reaction by treatment regimen		
	Rosiglitazone monotherapy	**Rosiglitazone with metformin**	**Rosiglitazone with metformin and sulphonylurea**
Blood and the lymphatic system disorders			
anaemia	Common	Common	Common
granulocytopaenia			Common
Metabolism and nutrition disorders			
hypercholesterolaemia[1]	Common	Common	Common
hypertriglyceridaemia	Common		
hyperlipaemia	Common	Common	Common
weight increase	Common	Common	Common
increased appetite	Common		
hypoglycaemia		Common	Very common
Nervous system disorders			
dizziness*		Common	
headache*			Common
Cardiac disorders			
cardiac failure[2]		Common	Common
cardiac ischaemia[3]*	Common	Common	Common
Gastrointestinal disorders			
constipation	Common	Common	Common
Musculoskeletal and connective tissue disorders			
bone fractures[4]	Common	Common	
myalgia*			Common
General disorders and administration site conditions			
oedema	Common	Common	Very common

*The frequency category for the background incidence of these events, as taken from placebo group data from clinical trials, is 'common'.

[1] Hypercholesterolaemia was reported in up to 5.3% of patients treated with rosiglitazone (monotherapy, dual or triple oral therapy). The elevated total cholesterol levels were associated with an increase in both LDLc and HDLc, but the ratio of total cholesterol: HDLc was unchanged or improved in long term studies. Overall, these increases were generally mild to moderate and usually did not require discontinuation of treatment.

[2] An increased incidence of heart failure has been observed when rosiglitazone was added to treatment regimens with a sulphonylurea (either as dual or triple therapy), and appeared higher with 8 mg rosiglitazone compared to 4 mg rosiglitazone (total daily dose). The incidence of heart failure on triple oral therapy was 1.4% in the main double blind study, compared to 0.4% for metformin plus sulphonylurea dual therapy. The incidence of heart failure in combination with insulin (rosiglitazone added to established insulin therapy) was 2.4%, compared to insulin alone, 1.1%.

In a placebo-controlled one-year trial in patients with congestive heart failure NYHA class I-II, worsening or possible worsening of heart failure occurred in 6.4% of patients treated with rosiglitazone, compared with 3.5% on placebo.

Medicinal product no longer authorised

[3] In a retrospective analysis of data from 42 pooled short-term clinical studies, the overall incidence of events typically associated with cardiac ischaemia was higher for rosiglitazone containing regimens, 2.00% versus combined active and placebo comparators, 1.53% [hazard ratio (HR) 1.30 (95% confidence interval (CI) 1.004 - 1.69)]. This risk was increased when rosiglitazone was added to established insulin and in patients receiving nitrates for known ischaemic heart disease. In an update to this retrospective analysis that included 10 further studies that met the criteria for inclusion, but were not available at the time of the original analysis, the overall incidence of events typically associated with cardiac ischaemia was not statistically different for rosiglitazone containing regimens, 2.21% versus combined active and placebo comparators, 2.08% [HR 1.098 (95% CI 0.809 - 1.354)]. In a prospective cardiovascular outcomes study (mean follow-up 5.5 years) the primary endpoint events of cardiovascular death or hospitalisation were similar between rosiglitazone and active comparators [HR 0.99 (95% CI 0.85 - 1.16)]. Two other long-term prospective randomised controlled clinical trials (9,620 patients, study duration >3 years in each study), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded the potential risk of cardiac ischaemia. In their entirety, the available data on the risk of cardiac ischaemia are inconclusive.

[4] Long-term studies show an increased incidence of bone fracture in patients, particularly female patients, taking rosiglitazone. In a monotherapy study, the incidence in females for rosiglitazone was 9.3% (2.7 patients per 100 patient years) vs 5.1% (1.5 patients per 100 patient years) for metformin or 3.5% (1.3 patients per 100 patient years) for glibenclamide. In another long-term study, there was an increased incidence of bone fracture for subjects in the combined rosiglitazone group compared to active control [8.3% vs 5.3%, Risk ratio 1.57 (95% CI 1.26 - 1.97)]. The risk of fracture appeared to be higher in females relative to control [11.5% vs 6.3%, Risk ratio 1.82 (95% CI 1.37 - 2.41)], than in males relative to control [5.3% vs 4.3%, Risk ratio 1.23 (95% CI 0.85 - 1.77)]. Additional data are necessary to determine whether there is an increased risk of fracture in males after a longer period of follow-up. The majority of the fractures were reported in the upper limbs and distal lower limbs (see section 4.4).

In double-blind clinical trials 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/sulphonylureas). The incidence of all adverse events relating to liver and biliary systems was <1.5% in any treatment group and similar to placebo.

Post-marketing data

In addition to the adverse reactions identified from clinical trial data, the adverse reactions presented in Table 2 have been identified in post approval use of rosiglitazone.

Medicinal product no longer authorised

Table 2. The frequency of adverse reactions identified from post-marketing data with rosiglitazone

Adverse reaction	**Frequency**
Metabolism and nutrition disorders	
rapid and excessive weight gain	Very rare
Immune system disorders (see Skin and subcutaneous tissue disorders)	
anaphylactic reaction	Very rare
Eye disorders	
macular oedema	Rare
Cardiac disorders	
congestive heart failure/pulmonary oedema	Rare
Hepatobiliary disorders	
hepatic dysfunction, primarily evidenced by elevated hepatic enzymes[5]	Rare
Skin and subcutaneous tissue disorders (see Immune system disorders)	
angioedema	Very rare
skin reactions (e.g. urticaria, pruritis, rash)	Very rare

[5] Rare cases of elevated liver enzymes and hepatocellular dysfunction have been reported. In very rare cases, a fatal outcome has been reported.

Metformin

Clinical Trial Data and Post-marketing data

Table 3 presents adverse reactions by system organ class and by frequency category. Frequency categories are based on information available from metformin Summary of Product Characteristics available in the EU.

Medicinal product no longer authorised

Table 3. The frequency of metformin adverse reactions identified from clinical trial and post-marketing data

Adverse reaction	Frequency
Gastrointestinal disorders	
gastrointestinal symptoms[6]	Very common
Metabolism and nutrition disorders	
lactic acidosis	Very rare
vitamin B12 deficiency[7]	Very rare
Nervous system disorders	
metallic taste	Common
Hepatobiliary disorders	
liver function disorders	Very rare
Hepatitis	Very rare
Skin and subcutaneous disorders	
urticaria	Very rare
erythema	Very rare
pruritis	Very rare

[6] Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

[7] Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g. megaloblastic anaemia).

4.9 Overdose

No data are available with regard to overdose of AVANDAMET.

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

A large overdose of metformin (or coexisting risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital.

In the event of an overdose, it is recommended that appropriate supportive treatment is 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of oral blood glucose lowering medicinal products, ATC code: A10BD03

AVANDAMET combines two antihyperglycaemic agents with complimentary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: rosiglitazone maleate, a member of the

Medicinal product no longer authorised

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.

Rosiglitazone
Rosiglitazone is a selective agonist at the PPARγ (peroxisome proliferator activated receptor gamma) nuclear receptor and is a member of the thiazolidinedione class of antihyperglycaemic agents. It reduces glycaemia by reducing insulin resistance at adipose tissue, skeletal muscle and liver.

The antihyperglycaemic activity of rosiglitazone has been demonstrated in a number of animal 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 animal models of type 2 diabetes. Rosiglitazone did not stimulate pancreatic insulin secretion or induce hypoglycaemia in rats and mice. The major metabolite (a para-hydroxy-sulphate) with high affinity to the soluble human PPARγ, exhibited relatively high potency in a glucose tolerance assay in obese mice. The clinical relevance of this observation has not been fully elucidated.

In clinical trials, the glucose lowering effects observed with rosiglitazone are gradual in onset with near maximal reductions in fasting plasma glucose (FPG) evident following approximately 8 weeks of therapy. The improved glycaemic control is associated with reductions in both fasting and post-prandial glucose.

Rosiglitazone was associated with increases in weight. In mechanistic studies, the weight increase was predominantly shown to be due to increased subcutaneous fat with decreased visceral and intra-hepatic fat.

Consistent with the mechanism of action, rosiglitazone in combination with metformin reduced insulin resistance and improved pancreatic ß-cell function. Improved glycaemic control was also associated with significant decreases in free fatty acids. As a consequence of different but complementary mechanisms of action, combination therapy of rosiglitazone with metformin resulted in additive effects on glycaemic control in type 2 diabetic patients.

In studies with a maximal duration of three years, rosiglitazone given once or twice daily in dual oral therapy with metformin produced a sustained improvement in glycaemic control (FPG and HbA1c). A more pronounced glucose-lowering effect was observed in obese patients. An outcome study has not been completed with rosiglitazone, therefore the long-term benefits associated with improved glycaemic control of rosiglitazone have not been demonstrated.

An active controlled clinical trial (rosiglitazone up to 8 mg daily or metformin up to 2,000 mg daily) of 24 weeks duration was performed in 197 children (10-17 years of age) with type 2 diabetes. Improvement in HbA1c from baseline achieved statistical significance only in the metformin group. Rosiglitazone failed to demonstrate non-inferiority to metformin. Following rosiglitazone treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. No long-term efficacy and safety data are available in paediatric patients.

ADOPT (A Diabetes Outcome Progression Trial) was a multicentre, double-blind, controlled trial with a treatment duration of 4-6 years (median duration of 4 years), in which rosiglitazone at doses of 4 to 8 mg/day was compared to metformin (500 mg to 2000 mg/day) and glibenclamide (2.5 to 15 mg/day) in 4351 drug naive subjects recently diagnosed (≤3 years) with type 2 diabetes. Rosiglitazone treatment significantly reduced the risk of reaching monotherapy failure (FPG>10.0 mmol/L) by 63% relative to glibenclamide (HR 0.37, CI 0.30-0.45) and by 32% relative to metformin (HR 0.68, CI 0.55-0.85) during the course of the study (up to 72 months of treatment). This translates to a cumulative incidence of treatment failure of 10.3% for rosiglitazone, 14.8% for metformin and 23.3% for glibenclamide treated patients. Overall, 43%, 47% and 42% of subjects in the rosiglitazone, glibenclamide and metformin groups respectively withdrew due to reasons other than monotherapy failure. The impact of these findings on disease progression or on microvascular or macrovascular outcomes has not been determined (see section 4.8). In this study, the adverse events observed were

Medicinal product no longer authorised

consistent with the known adverse event profile for each of the treatments, including continuing weight gain with rosiglitazone. An additional observation of an increased incidence of bone fractures was seen in women with rosiglitazone (see sections 4.4 and 4.8).

The RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) trial was a large (4,447 subjects), open-label, prospective, controlled study (mean follow-up 5.5 years) in which patients with type 2 diabetes inadequately controlled with metformin or sulphonylurea were randomised to add-on rosiglitazone or metformin or sulphonylurea. The mean duration of diabetes in these patients was approximately 7 years. The adjudicated primary endpoint was cardiovascular hospitalisation (which included hospitalisations for heart failure) or cardiovascular death. Mean doses at the end of randomised treatment are shown in the following table:

Randomised Treatment†	**Mean (SD) dose at end of randomised treatment**
Rosiglitazone (either SU or metformin)	6.7 (1.9) mg
Sulphonylurea (background metformin)	
Glimepiride*	3.6 (1.8) mg
Metformin (background sulphonylurea)	1995.5 (682.6) mg

*Similar relative effective doses (i.e approximately half maximal dose) for other sulphonylureas (glibenclamide and glicazide).
† Patients who took designated treatment as randomised in combination with the correct background treatment and with evaluable data.

No difference in the number of adjudicated primary endpoint events for rosiglitazone (321/2220) versus active control (323/2227) (HR 0.99, CI 0.85-1.16) was observed, meeting the pre-defined non-inferiority criterion of 1.20 (non-inferiority p = 0.02). HR and CI for key secondary endpoints were: all-cause death (HR 0.86, CI 0.68-1.08), MACE (Major Adverse Cardiac Events - cardiovascular death, acute myocardial infarction, stroke) (HR 0.93, CI 0.74-1.15), cardiovascular death (HR 0.84, CI 0.59-1.18), acute myocardial infarction (HR 1.14, CI 0.80-1.63) and stroke (HR 0.72, CI 0.49-1.06). In a sub-study at 18 months, add-on rosiglitazone dual therapy was non-inferior to the combination of sulphonylurea plus metformin for lowering HbA1c. In the final analysis at 5 years, an adjusted mean reduction from baseline in HbA1c of 0.14% for patients on rosiglitazone added to metformin versus an increase of 0.17% for patients taking sulphonylurea added to metformin was seen during treatment with randomised dual-combination therapy ($p<0.0001$ for treatment difference). An adjusted mean reduction in HbA1c of 0.24% was seen for patients taking rosiglitazone added to sulphonylurea, versus a reduction in HbA1c of 0.10% for patients taking metformin added to sulphonylurea, ($p=0.0083$ for treatment difference). There was a significant increase in heart failure (fatal and non-fatal) (HR 2.10, CI 1.35-3.27) and bone fractures (Risk Ratio 1.57, CI 1.26-1.97) in rosiglitazone-containing treatments compared to active control (see sections 4.4 and 4.8). A total of 564 patients withdrew from cardiovascular follow-up, which accounted for 12.3% of rosiglitazone patients and 13% of control patients; representing 7.2% of patient-years lost for cardiovascular events follow-up and 2.0% of patient-years lost for all cause mortality follow-up.

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 three 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).

Medicinal product no longer authorised

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, LDLc and triglyceride levels.

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034
- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021)
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years (p=0.01).

5.2 Pharmacokinetic properties

AVANDAMET

Absorption

No statistically significant difference was observed between the absorption characteristics of rosiglitazone and metformin from the AVANDAMET tablet and those obtained from rosiglitazone maleate and metformin hydrochloride tablets, respectively.

Food had no effect on the AUC of rosiglitazone or metformin when AVANDAMET was administered to healthy volunteers. In the fed state, C_{max} was lower (22% rosiglitazone and 15% metformin) and t_{max} delayed (by approximately 1.5 h rosiglitazone and 0.5 h metformin). This food-effect is not considered clinically significant.

The following statements reflect the pharmacokinetic properties of the individual active substances of AVANDAMET.

Rosiglitazone

Absorption

Absolute bioavailability of rosiglitazone following both a 4 and an 8 mg oral dose is approximately 99%. Rosiglitazone plasma concentrations peak at around 1 h after dosing. Plasma concentrations 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 C_{max} (approximately 20-28%) and a delay in t_{max} (approximately 1.75 h) were observed compared to dosing in the fasting 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.

Distribution

The volume of distribution of rosiglitazone is approximately 14 l in healthy volunteers. Plasma protein binding of rosiglitazone is high (approximately 99.8%) and is not influenced by concentration or age. The protein binding of the major metabolite (a para-hydroxy-sulphate) is very high (> 99.99%).

Metabolism

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 contribution of the major metabolite (a para-hydroxy-sulphate) to

Medicinal product no longer authorised

the overall antihyperglycaemic activity of rosiglitazone has not been fully elucidated in man and it cannot be ruled out that the metabolite may contribute to the activity. However, this raises no safety concern regarding target or special populations as hepatic impairment is contraindicated and the phase III clinical studies included a considerable number of elderly patients and patients with mild to moderate renal impairment.

In vitro studies demonstrate that rosiglitazone is predominantly metabolised by CYP2C8, with a minor contribution by CYP2C9.

Since there is no significant *in vitro* inhibition of CYP1A2, 2A6, 2C19, 2D6, 2E1, 3A or 4A with rosiglitazone, there is a low probability of significant metabolism-based interactions with substances metabolised by these P450 enzymes. Rosiglitazone showed moderate inhibition of CYP2C8 (IC_{50} 18 μM) and low inhibition of CYP2C9 (IC_{50} 50 μM) *in vitro* (see section 4.5). An *in vivo* interaction study with warfarin indicated that rosiglitazone does not interact with CYP2C9 substrates *in vivo*.

Elimination

Total plasma clearance of rosiglitazone is around 3 l/h and the terminal elimination half-life of rosiglitazone is approximately 3-4 h. There is no evidence for unexpected accumulation of rosiglitazone after once or twice daily dosing. The major route of excretion is the urine with approximately two-thirds of the dose being eliminated by this route, whereas faecal elimination accounts for approximately 25% of dose. No intact active substance is excreted in urine or faeces. The terminal half-life for radioactivity was about 130 h indicating that elimination of metabolites is very slow. Accumulation of the metabolites in plasma is expected upon repeated dosing, especially that of the major metabolite (a para-hydroxy-sulphate) for which an 8-fold accumulation is anticipated.

Special populations

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.

Children and adolescents: Population pharmacokinetic analysis including 96 paediatric patients aged 10 to 18 years and weighing 35 to 178 kg suggested similar mean CL/F in children and adults. Individual CL/F in the paediatric population was in the same range as individual adult data. CL/F seemed to be independent of age, but increased with weight in the paediatric population.

Hepatic impairment: In cirrhotic patients with moderate (Child-Pugh B) hepatic impairment, unbound C_{max} and AUC were 2- and 3-fold higher than in normal subjects. The inter-subject variability was large, with a 7-fold difference in unbound AUC between patients.

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.

Metformin

Absorption

After an oral dose of metformin, t_{max} is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 μg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 μg/ml, even at maximum doses.

Medicinal product no longer authorised

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Distribution
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean V_d ranged between 63 – 276 l.

Metabolism
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination
Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3 Preclinical safety data

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
Undesirable effects observed in animal studies with possible relevance to clinical use were as follows: An increase in plasma volume accompanied by decrease in red cell parameters and increase in heart weight. Increases in liver weight, plasma ALT (dog only) and fat tissue were also observed. Similar effects have been seen with other thiazolidinediones.

In reproductive toxicity studies, administration of rosiglitazone to rats during mid-late gestation was associated with foetal death and retarded foetal development. In addition, rosiglitazone inhibited ovarian oestradiol and progesterone synthesis and lowered plasma levels of these hormones resulting in effects on oestrus/menstrual cycles and fertility (see section 4.4).

In an animal model for familial adenomatous polyposis (FAP), treatment with rosiglitazone at 200 times the pharmacologically active dose increased tumour multiplicity in the colon. The relevance of this finding is unknown. However, rosiglitazone promoted differentiation and reversal of mutagenic changes in human colon cancer cells *in vitro*. In addition, rosiglitazone was not genotoxic in a battery of *in vivo* and *in vitro* genotoxicity studies and there was no evidence of colon tumours in lifetime studies of rosiglitazone in two rodent species.

Metformin
Non-clinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Sodium starch glycollate
Hypromellose (E464)
Microcrystalline cellulose (E460)

Medicinal product no longer authorised

Lactose monohydrate
Povidone (E1201)
Magnesium stearate.

Film coat:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol
Iron oxide yellow (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Opaque blisters (PVC/PVdC/aluminium). Packs of 28, 56, 112, 336 (3x112) and 360 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/001-003
EU/1/03/258/015
EU/1/03/258/019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 October 2003
Date of latest renewal: 20 October 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.ema.europa.eu

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 2 mg/500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of rosiglitazone (as rosiglitazone maleate) and 500 mg of metformin hydrochloride (corresponding to metformin free base 390 mg).

Excipients:
Each tablet contains lactose (approximately 11 mg)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pale pink film-coated tablets marked "gsk" on one side and "2/500" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AVANDAMET is indicated in the treatment of type 2 diabetes mellitus patients, particularly overweight patients:

- who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone.
- in triple oral therapy with sulphonylurea in patients with insufficient glycaemic control despite dual oral therapy with their maximally tolerated dose of metformin and a sulphonylurea (see section 4.4).

4.2 Posology and method of administration

The usual starting dose of AVANDAMET is 4 mg/day rosiglitazone plus 2000 mg/day metformin hydrochloride.

Rosiglitazone can be increased to 8 mg/day after 8 weeks if greater glycaemic control is required. The maximum recommended daily dose of AVANDAMET is 8 mg rosiglitazone plus 2000 mg metformin hydrochloride.

The total daily dose of AVANDAMET should be given in two divided doses.

Dose titration with rosiglitazone (added to the optimal dose of metformin) may be considered before the patient is switched to AVANDAMET.

When clinically appropriate, direct change from metformin monotherapy to AVANDAMET may be considered.

Taking AVANDAMET with or just after food may reduce gastrointestinal symptoms associated with metformin.

Triple oral therapy (rosiglitazone, metformin and sulphonylurea) (see section 4.4)

Medicinal product no longer authorised

- Patients on metformin and sulphonylurea: when appropriate AVANDAMET may be initiated at 4 mg/day rosiglitazone with the dose of metformin substituting that already being taken. An increase in the rosiglitazone component to 8 mg/day should be undertaken cautiously following appropriate clinical evaluation to assess the patient's risk of developing adverse reactions relating to fluid retention (see sections 4.4 and 4.8).
- Patients established on triple oral therapy: when appropriate, AVANDAMET may substitute rosiglitazone and metformin doses already being taken.

Where appropriate, AVANDAMET may be used to substitute concomitant rosiglitazone and metformin in existing dual or triple oral therapy to simplify treatment.

Elderly
As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking AVANDAMET should have their renal function monitored regularly (see sections 4.3 and 4.4).

Patients with renal impairment
AVANDAMET should not be used in patients with renal failure or renal dysfunction e.g. serum creatinine levels > 135 µmol/l in males and > 110 µmol/l in females and/or creatinine clearance < 70 ml/min (see sections 4.3 and 4.4).

Children and adolescents
AVANDAMET is not recommended for use in children and adolescents below 18 years of age as there are no data available on its safety and efficacy in this age group (see sections 5.1 and 5.2).

4.3 Contraindications

AVANDAMET is contraindicated in patients with:

- hypersensitivity to rosiglitazone, metformin hydrochloride or to any of the excipients
- cardiac failure or history of cardiac failure (New York Heart Association (NYHA) stages I to IV)
- an Acute Coronary Syndrome (unstable angina, NSTEMI and STEMI) (see section 4.4)
- acute or chronic disease which may cause tissue hypoxia such as:
    - cardiac or respiratory failure
    - recent myocardial infarction
    - shock
- hepatic impairment
- acute alcohol intoxication, alcoholism (see section 4.4)
- diabetic ketoacidosis or diabetic pre-coma
- renal failure or renal dysfunction e.g. serum creatinine levels > 135 µmol/l in males and > 110 µmol/l in females and/or creatinine clearance < 70 ml/min (see section 4.4)
- acute conditions with the potential to alter renal function such as:
    - dehydration
    - severe infection
    - shock
    - intravascular administration of iodinated contrast agents (see section 4.4)
    - lactation.

4.4 Special warnings and precautions for use

Lactic acidosis
Lactic acidosis is a very rare, but serious, metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis,

Medicinal product no longer authorised

prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia.

Diagnosis:
Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/l and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately (see section 4.9).

Renal function
As metformin is excreted by the kidney, serum creatinine concentrations should be determined regularly:
- at least once a year in patients with normal renal function
- at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly patients.

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with an NSAID.

Fluid retention and cardiac failure
Thiazolidinediones can cause fluid retention which may exacerbate or precipitate signs or symptoms of congestive heart failure. Rosiglitazone can cause dose-dependent fluid retention. The possible contribution of fluid retention to weight gain should be individually assessed as rapid and excessive weight gain has been reported very rarely as a sign of fluid retention. All patients, particularly those receiving concurrent insulin but also sulphonylurea therapy, those at risk for heart failure, and those with reduced cardiac reserve, should be monitored for signs and symptoms of adverse reactions relating to fluid retention, including weight gain and heart failure. AVANDAMET must be discontinued if any deterioration in cardiac status occurs.

The use of AVANDAMET in combination with a sulphonylurea or insulin may be associated with increased risks of fluid retention and heart failure (see section 4.8). The decision to initiate AVANDAMET in combination with a sulphonylurea should include consideration of alternative therapies. Increased monitoring of the patient is recommended if AVANDAMET is used in combination particularly with insulin but also with a sulphonylurea.

Heart failure was also reported more frequently in patients with a history of heart failure; oedema and heart failure was also reported more frequently in elderly patients and in patients with mild or moderate renal failure. Caution should be exercised in patients over 75 years because of the limited experience in this patient group. Since NSAIDs, insulin and rosiglitazone are all associated with fluid retention, concomitant administration may increase the risk of oedema.

Combination with insulin
An increased incidence of cardiac failure has been observed in clinical trials when rosiglitazone is 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. Insulin should only be added to established rosiglitazone therapy in exceptional cases and under close supervision.

Myocardial Ischaemia
A retrospective analysis of data from 42 pooled short-term clinical studies indicated that treatment with rosiglitazone may be associated with an increased risk of myocardial ischaemic events. However, in their entirety the available data on the risk of cardiac ischaemia are inconclusive (see section 4.8). There are limited clinical trial data in patients with ischaemic heart disease and/or peripheral arterial disease. Therefore, as a precaution, the use of rosiglitazone is not recommended in these patients, particularly those with myocardial ischaemic symptoms.

Medicinal product no longer authorised

Acute Coronary Syndrome (ACS)
Patients experiencing an ACS have not been studied in rosiglitazone controlled clinical trials. In view of the potential for development of heart failure in these patients, rosiglitazone should therefore not be initiated in patients having an acute coronary event and it should be discontinued during the acute phase (see section 4.3).

Monitoring of liver function
There have been rare reports of hepatocellular dysfunction during post-marketing experience with rosiglitazone (see section 4.8). There is limited experience with rosiglitazone in patients with elevated liver enzymes (ALT > 2.5 times the upper limit of normal). Therefore, liver enzymes should be checked prior to the initiation of therapy with AVANDAMET in all patients and periodically thereafter based on clinical judgement. Therapy with AVANDAMET should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 times the upper limit of normal) or with any other evidence of liver disease. If ALT levels are increased to > 3 times the upper limit of normal during AVANDAMET therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 times the upper limit of normal, therapy 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, therapy should be discontinued.

Eye disorders
Post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with thiazolidinediones, including rosiglitazone. Many of these patients reported concurrent peripheral oedema. It is unclear whether or not there is a direct association between rosiglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity and appropriate ophthalmologic referral should be considered.

Weight gain
In clinical trials with rosiglitazone there was evidence of dose-related weight gain, which was greater when used in combination with insulin. Therefore weight should be closely monitored, given that it may be attributable to fluid retention, which may be associated with cardiac failure.

Anaemia
Rosiglitazone treatment is associated with a dose-related reduction of haemoglobin levels. In patients with low haemoglobin levels before initiating therapy, there is an increased risk of anaemia during treatment with AVANDAMET.

Hypoglycaemia
Patients receiving AVANDAMET in combination with a sulphonylurea or insulin may be at risk for dose-related hypoglycaemia. Increased monitoring of the patient and a reduction in the dose of the concomitant agent may be necessary.

Surgery
As AVANDAMET contains metformin hydrochloride, the treatment should be discontinued 48 hours before elective surgery with general anaesthesia and should not usually be resumed earlier than 48 hours afterwards.

Administration of iodinated contrast agent
The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure. Therefore, due to the metformin active substance, AVANDAMET should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.5).

Bone disorders

Medicinal product no longer authorised

Long-term studies show an increased incidence of bone fractures in patients, particularly female patients, taking rosiglitazone (see section 4.8). The majority of the fractures have occurred in the upper limbs and distal lower limbs. In females, this increased incidence was noted after the first year of treatment and persisted during long-term treatment. The risk of fracture should be considered in the care of patients, especially female patients, treated with rosiglitazone.

Other precautions
Premenopausal women have received rosiglitazone during clinical studies. Although hormonal imbalance has been seen in preclinical studies (see section 5.3), no significant undesirable effects associated with menstrual disorders have been observed. As a consequence of improving insulin sensitivity, resumption of ovulation may occur in patients who are anovulatory due to insulin resistance. Patients should be aware of the risk of pregnancy (see section 4.6).

AVANDAMET should be used with caution during concomitant administration of CYP2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin), due to the effect on rosiglitazone pharmacokinetics (see section 4.5). Furthermore, AVANDAMET should be used with caution during concomitant administration of cationic medicinal products that are eliminated by renal tubular secretion (e.g. cimetidine) due to the effect on metformin pharmacokinetics (see section 4.5). Glycaemic control should be monitored closely. AVANDAMET dose adjustment within the recommended posology or changes in diabetic treatment should be considered.

All patients should continue their diet with regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
The usual laboratory tests for diabetes monitoring should be performed regularly.

AVANDAMET tablets contain lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for AVANDAMET, however the concomitant use of the active substances in patients in clinical studies and in widespread clinical use has not resulted in any unexpected interactions. The following statements reflect the information available on the individual active substances (rosiglitazone and metformin).

There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic insufficiency) due to the metformin active substance of AVANDAMET (see section 4.4). Avoid consumption of alcohol and medicinal products containing alcohol.

Cationic medicinal products that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and C_{max} by 81%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered (see section 4.4).

In vitro studies demonstrate that rosiglitazone is predominantly metabolised by CYP2C8, with CYP2C9 as only a minor pathway.

Co-administration of rosiglitazone with gemfibrozil (an inhibitor of CYP2C8) resulted in a twofold increase in rosiglitazone plasma concentrations. Since there is a potential for an increase in the risk of dose-related adverse reactions, a decrease in rosiglitazone dose may be needed. Close monitoring of glycaemic control should be considered (see section 4.4).

Medicinal product no longer authorised

Co-administration of rosiglitazone with rifampicin (an inducer of CYP2C8) resulted in a 66% decrease in rosiglitazone plasma concentrations. It cannot be excluded that other inducers (e.g. phenytoin, carbamazepine, phenobarbital, St John's wort) may also affect rosiglitazone exposure. The rosiglitazone dose may need to be increased. Close monitoring of glycaemic control should be considered (see section 4.4).

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

Concomitant administration of rosiglitazone with the oral antihyperglycaemic agents glibenclamide and acarbose did not result in any clinically relevant pharmacokinetic interactions.

No clinically relevant interactions with digoxin, the CYP2C9 substrate warfarin, the CYP3A4 substrates nifedipine, ethinylestradiol or norethindrone were observed after co-administration with rosiglitazone.

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.

Combination requiring precautions for use
Glucocorticoids (given by systemic and local routes) beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment. If necessary, the dosage of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.
ACE-inhibitors may decrease the blood glucose levels. If necessary, the dosage of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

4.6 Pregnancy and lactation

For AVANDAMET no preclinical or clinical data on exposed pregnancies or lactation are available.

Rosiglitazone has been reported to cross the human placenta and to be detectable in foetal tissues. There are no adequate data from the use of rosiglitazone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Therefore, AVANDAMET should not be used during pregnancy. If a patient wishes to become pregnant or if pregnancy occurs, treatment with AVANDAMET should be discontinued unless the expected benefit to the mother outweighs the potential risk to the foetus.

Both rosiglitazone and metformin have been detected in the milk of experimental animals. It is not known whether breast-feeding will lead to exposure of the infant to the medicinal product. AVANDAMET must therefore not be used in women who are breast-feeding (see section 4.3).

4.7 Effects on ability to drive and use machines

AVANDAMET has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are presented below for each of the component parts of AVANDAMET. An adverse reaction is only presented for the fixed dose combination if it has not been seen in one of the component parts of AVANDAMET or if it occurred at a higher frequency than that listed for a component part.

Medicinal product no longer authorised

Adverse reactions for each treatment regimen are presented below by system organ class and absolute frequency. For dose-related adverse reactions the frequency category reflects the higher dose of rosiglitazone. Frequency categories do not account for other factors including varying study duration, pre-existing conditions and baseline patient characteristics. Adverse reaction frequency categories assigned based on clinical trial experience may not reflect the frequency of adverse events occurring during normal clinical practice. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000 including isolated reports).

AVANDAMET

Data from double-blind studies confirm that the safety profile of concomitant rosiglitazone and metformin is similar to that of the combined adverse reaction profile for the two medicinal products. Data with AVANDAMET is also consistent with this combined adverse reaction profile.

Clinical trial data (addition of insulin to established AVANDAMET therapy)
In a single study (n=322) where insulin was added to patients established on AVANDAMET, no new adverse events were observed in excess of those already defined for either AVANDAMET or rosiglitazone combination therapies.
However, the risk of both fluid related adverse events and hypoglycaemia are increased when AVANDAMET is used in combination with insulin.

Rosiglitazone

Clinical trial data
Adverse reactions for each treatment regimen are presented below by system organ class and absolute frequency. For dose-related adverse reactions the frequency category reflects the higher dose of rosiglitazone. Frequency categories do not account for other factors including varying study duration, pre-existing conditions and baseline patient characteristics.

Table 1 lists adverse reactions identified from an overview of clinical trials involving over 5,000 rosiglitazone-treated patients. Within each system organ class, adverse reactions are presented in the table by decreasing frequency for the rosiglitazone monotherapy treatment regimen. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Medicinal product no longer authorised

Table 1. The frequency of adverse reactions identified from clinical trial data with rosiglitazone

Adverse reaction	Frequency of adverse reaction by treatment regimen		
	Rosiglitazone monotherapy	**Rosiglitazone with metformin**	**Rosiglitazone with metformin and sulphonylurea**
Blood and the lymphatic system disorders			
Anaemia	Common	Common	Common
granulocytopaenia			Common
Metabolism and nutrition disorders			
hypercholesterolaemia[1]	Common	Common	Common
hypertriglyceridaemia	Common		
Hyperlipaemia	Common	Common	Common
weight increase	Common	Common	Common
increased appetite	Common		
Hypoglycaemia		Common	Very common
Nervous system disorders			
dizziness*		Common	
headache*			Common
Cardiac disorders			
cardiac failure[2]		Common	Common
cardiac ischaemia[3]*	Common	Common	Common
Gastrointestinal disorders			
Constipation	Common	Common	Common
Musculoskeletal and connective tissue disorders			
bone fractures[4]	Common	Common	
myalgia*			Common
General disorders and administration site conditions			
Oedema	Common	Common	Very common

*The frequency category for the background incidence of these events, as taken from placebo group data from clinical trials, is 'common'.

[1] Hypercholesterolaemia was reported in up to 5.3% of patients treated with rosiglitazone (monotherapy, dual or triple oral therapy). The elevated total cholesterol levels were associated with an increase in both LDLc and HDLc, but the ratio of total cholesterol: HDLc was unchanged or improved in long term studies. Overall, these increases were generally mild to moderate and usually did not require discontinuation of treatment.

[2] An increased incidence of heart failure has been observed when rosiglitazone was added to treatment regimens with a sulphonylurea (either as dual or triple therapy), and appeared higher with 8 mg rosiglitazone compared to 4 mg rosiglitazone (total daily dose). The incidence of heart failure on triple oral therapy was 1.4% in the main double blind study, compared to 0.4% for metformin plus sulphonylurea dual therapy. The incidence of heart failure in combination with insulin (rosiglitazone added to established insulin therapy) was 2.4%, compared to insulin alone, 1.1%.

In a placebo-controlled one-year trial in patients with congestive heart failure NYHA class I-II, worsening or possible worsening of heart failure occurred in 6.4% of patients treated with rosiglitazone, compared with 3.5% on placebo.

Medicinal product no longer authorised

[3] In a retrospective analysis of data from 42 pooled short-term clinical studies, the overall incidence of events typically associated with cardiac ischaemia was higher for rosiglitazone containing regimens, 2.00% versus combined active and placebo comparators, 1.53% [hazard ratio (HR) 1.30 (95% confidence interval (CI) 1.004 - 1.69)]. This risk was increased when rosiglitazone was added to established insulin and in patients receiving nitrates for known ischaemic heart disease. In an update to this retrospective analysis that included 10 further studies that met the criteria for inclusion, but were not available at the time of the original analysis, the overall incidence of events typically associated with cardiac ischaemia was not statistically different for rosiglitazone containing regimens, 2.21% versus combined active and placebo comparators, 2.08% [HR 1.098 (95% CI 0.809 - 1.354)]. In a prospective cardiovascular outcomes study (mean follow-up 5.5 years) the primary endpoint events of cardiovascular death or hospitalisation were similar between rosiglitazone and active comparators [HR 0.99 (95% CI 0.85 - 1.16)]. Two other long-term prospective randomised controlled clinical trials (9,620 patients, study duration >3 years in each study), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded the potential risk of cardiac ischaemia. In their entirety, the available data on the risk of cardiac ischaemia are inconclusive.

[4] Long-term studies show an increased incidence of bone fracture in patients, particularly female patients, taking rosiglitazone. In a monotherapy study, the incidence in females for rosiglitazone was 9.3% (2.7 patients per 100 patient years) vs 5.1% (1.5 patients per 100 patient years) for metformin or 3.5% (1.3 patients per 100 patient years) for glibenclamide. In another long-term study, there was an increased incidence of bone fracture for subjects in the combined rosiglitazone group compared to active control [8.3% vs 5.3%, Risk ratio 1.57 (95% CI 1.26 - 1.97)]. The risk of fracture appeared to be higher in females relative to control [11.5% vs 6.3%, Risk ratio 1.82 (95% CI 1.37 - 2.41)], than in males relative to control [5.3% vs 4.3%, Risk ratio 1.23 (95% CI 0.85 - 1.77)]. Additional data are necessary to determine whether there is an increased risk of fracture in males after a longer period of follow-up. The majority of the fractures were reported in the upper limbs and distal lower limbs (see section 4.4).

In double-blind clinical trials 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/sulphonylureas). The incidence of all adverse events relating to liver and biliary systems was <1.5% in any treatment group and similar to placebo.

Post-marketing data

In addition to the adverse reactions identified from clinical trial data, the adverse reactions presented in Table 2 have been identified in post approval use of rosiglitazone.

Medicinal product no longer authorised

Table 2. The frequency of adverse reactions identified from post-marketing data with rosiglitazone

Adverse reaction	**Frequency**
Metabolism and nutrition disorders	
rapid and excessive weight gain	Very rare
Immune system disorders (see Skin and subcutaneous tissue disorders)	
anaphylactic reaction	Very rare
Eye disorders	
macular oedema	Rare
Cardiac disorders	
congestive heart failure/pulmonary oedema	Rare
Hepatobiliary disorders	
hepatic dysfunction, primarily evidenced by elevated hepatic enzymes[5]	Rare
Skin and subcutaneous tissue disorders (see Immune system disorders)	
Angioedema	Very rare
skin reactions (e.g. urticaria, pruritis, rash)	Very rare

[5] Rare cases of elevated liver enzymes and hepatocellular dysfunction have been reported. In very rare cases, a fatal outcome has been reported.

Metformin

Clinical Trial Data and Post-marketing data

Table 3 presents adverse reactions by system organ class and by frequency category. Frequency categories are based on information available from metformin Summary of Product Characteristics available in the EU.

Medicinal product no longer authorised

Table 3. The frequency of metformin adverse reactions identified from clinical trial and post-marketing data

Adverse reaction	Frequency
Gastrointestinal disorders	
gastrointestinal symptoms[6]	Very common
Metabolism and nutrition disorders	
lactic acidosis	Very rare
vitamin B12 deficiency[7]	Very rare
Nervous system disorders	
metallic taste	Common
Hepatobiliary disorders	
liver function disorders	Very rare
Hepatitis	Very rare
Skin and subcutaneous disorders	
urticaria	Very rare
Erythema	Very rare
Pruritis	Very rare

[6] Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

[7] Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g. megaloblastic anaemia).

4.9 Overdose

No data are available with regard to overdose of AVANDAMET.
Limited data are available with regard to overdose of rosiglitazone in humans. In clinical studies in volunteers rosiglitazone has been administered at single oral doses of up to 20 mg and was well tolerated.

A large overdose of metformin (or coexisting risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital.

In the event of an overdose, it is recommended that appropriate supportive treatment is 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of oral blood glucose lowering medicinal products, ATC code: A10BD03

AVANDAMET combines two antihyperglycaemic agents with complimentary 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.

Medicinal product no longer authorised

Thiazolidinediones act primarily by reducing insulin resistance and biguanides act primarily by decreasing endogenous hepatic glucose production.

Rosiglitazone
Rosiglitazone is a selective agonist at the PPARγ (peroxisome proliferator activated receptor gamma) nuclear receptor and is a member of the thiazolidinedione class of antihyperglycaemic agents. It reduces glycaemia by reducing insulin resistance at adipose tissue, skeletal muscle and liver.

The antihyperglycaemic activity of rosiglitazone has been demonstrated in a number of animal 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 animal models of type 2 diabetes. Rosiglitazone did not stimulate pancreatic insulin secretion or induce hypoglycaemia in rats and mice. The major metabolite (a para-hydroxy-sulphate) with high affinity to the soluble human PPARγ, exhibited relatively high potency in a glucose tolerance assay in obese mice. The clinical relevance of this observation has not been fully elucidated.

In clinical trials, the glucose lowering effects observed with rosiglitazone are gradual in onset with near maximal reductions in fasting plasma glucose (FPG) evident following approximately 8 weeks of therapy. The improved glycaemic control is associated with reductions in both fasting and post-prandial glucose.

Rosiglitazone was associated with increases in weight. In mechanistic studies, the weight increase was predominantly shown to be due to increased subcutaneous fat with decreased visceral and intra-hepatic fat.

Consistent with the mechanism of action, rosiglitazone in combination with metformin reduced insulin resistance and improved pancreatic ß-cell function. Improved glycaemic control was also associated with significant decreases in free fatty acids. As a consequence of different but complementary mechanisms of action, combination therapy of rosiglitazone with metformin resulted in additive effects on glycaemic control in type 2 diabetic patients.

In studies with a maximal duration of three years, rosiglitazone given once or twice daily in dual oral therapy with metformin produced a sustained improvement in glycaemic control (FPG and HbA1c). A more pronounced glucose-lowering effect was observed in obese patients. An outcome study has not been completed with rosiglitazone, therefore the long-term benefits associated with improved glycaemic control of rosiglitazone have not been demonstrated.

An active controlled clinical trial (rosiglitazone up to 8 mg daily or metformin up to 2,000 mg daily) of 24 weeks duration was performed in 197 children (10-17 years of age) with type 2 diabetes. Improvement in HbA1c from baseline achieved statistical significance only in the metformin group. Rosiglitazone failed to demonstrate non-inferiority to metformin. Following rosiglitazone treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. No long-term efficacy and safety data are available in paediatric patients.

ADOPT (A Diabetes Outcome Progression Trial) was a multicentre, double-blind, controlled trial with a treatment duration of 4-6 years (median duration of 4 years), in which rosiglitazone at doses of 4 to 8 mg/day was compared to metformin (500 mg to 2000 mg/day) and glibenclamide (2.5 to 15 mg/day) in 4351 drug naive subjects recently diagnosed (≤3 years) with type 2 diabetes. Rosiglitazone treatment significantly reduced the risk of reaching monotherapy failure (FPG>10.0 mmol/L) by 63% relative to glibenclamide (HR 0.37, CI 0.30-0.45) and by 32% relative to metformin (HR 0.68, CI 0.55-0.85) during the course of the study (up to 72 months of treatment). This translates to a cumulative incidence of treatment failure of 10.3% for rosiglitazone, 14.8% for metformin and 23.3% for glibenclamide treated patients. Overall, 43%, 47% and 42% of subjects in the rosiglitazone, glibenclamide and metformin groups respectively withdrew due to reasons other than monotherapy failure. The impact of these findings on disease progression or on microvascular or macrovascular outcomes has not been determined (see section 4.8). In this study, the adverse events observed were consistent with the known adverse event profile for each of the treatments, including continuing

Medicinal product no longer authorised

weight gain with rosiglitazone. An additional observation of an increased incidence of bone fractures was seen in women with rosiglitazone (see sections 4.4 and 4.8).

The RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) trial was a large (4,447 subjects), open-label, prospective, controlled study (mean follow-up 5.5 years) in which patients with type 2 diabetes inadequately controlled with metformin or sulphonylurea were randomised to add-on rosiglitazone or metformin or sulphonylurea. The mean duration of diabetes in these patients was approximately 7 years. The adjudicated primary endpoint was cardiovascular hospitalisation (which included hospitalisations for heart failure) or cardiovascular death. Mean doses at the end of randomised treatment are shown in the following table:

Randomised Treatment†	**Mean (SD) dose at end of randomised treatment**
Rosiglitazone (either SU or metformin)	6.7 (1.9) mg
Sulphonylurea (background metformin)	
Glimepiride*	3.6 (1.8) mg
Metformin (background sulphonylurea)	1995.5 (682.6) mg

*Similar relative effective doses (i.e approximately half maximal dose) for other sulphonylureas (glibenclamide and glicazide).
† Patients who took designated treatment as randomised in combination with the correct background treatment and with evaluable data.

No difference in the number of adjudicated primary endpoint events for rosiglitazone (321/2220) versus active control (323/2227) (HR 0.99, CI 0.85-1.16) was observed, meeting the pre-defined non-inferiority criterion of 1.20 (non-inferiority p = 0.02). HR and CI for key secondary endpoints were: all-cause death (HR 0.86, CI 0.68-1.08), MACE (Major Adverse Cardiac Events - cardiovascular death, acute myocardial infarction, stroke) (HR 0.93, CI 0.74-1.15), cardiovascular death (HR 0.84, CI 0.59-1.18), acute myocardial infarction (HR 1.14, CI 0.80-1.63) and stroke (HR 0.72, CI 0.49-1.06). In a sub-study at 18 months, add-on rosiglitazone dual therapy was non-inferior to the combination of sulphonylurea plus metformin for lowering HbA1c. In the final analysis at 5 years, an adjusted mean reduction from baseline in HbA1c of 0.14% for patients on rosiglitazone added to metformin versus an increase of 0.17% for patients taking sulphonylurea added to metformin was seen during treatment with randomised dual-combination therapy ($p<0.0001$ for treatment difference). An adjusted mean reduction in HbA1c of 0.24% was seen for patients taking rosiglitazone added to sulphonylurea, versus a reduction in HbA1c of 0.10% for patients taking metformin added to sulphonylurea, ($p=0.0083$ for treatment difference). There was a significant increase in heart failure (fatal and non-fatal) (HR 2.10, CI 1.35-3.27) and bone fractures (Risk Ratio 1.57, CI 1.26-1.97) in rosiglitazone-containing treatments compared to active control (see sections 4.4 and 4.8). A total of 564 patients withdrew from cardiovascular follow-up, which accounted for 12.3% of rosiglitazone patients and 13% of control patients, representing 7.2% of patient-years lost for cardiovascular events follow-up and 2.0% of patient-years lost for all cause mortality follow-up.

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 three 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).

Medicinal product no longer authorised

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, LDLc and triglyceride levels.

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034
- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021)
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years (p=0.01).

5.2 Pharmacokinetic properties

AVANDAMET

Absorption

No statistically significant difference was observed between the absorption characteristics of rosiglitazone and metformin from the AVANDAMET tablet and those obtained from rosiglitazone maleate and metformin hydrochloride tablets, respectively.

Food had no effect on the AUC of rosiglitazone or metformin when AVANDAMET was administered to healthy volunteers. In the fed state, C_{max} was lower (22% rosiglitazone and 15% metformin) and t_{max} delayed (by approximately 1.5 h rosiglitazone and 0.5 h metformin). This food-effect is not considered clinically significant.

The following statements reflect the pharmacokinetic properties of the individual active substances of AVANDAMET.

Rosiglitazone

Absorption

Absolute bioavailability of rosiglitazone following both a 4 and an 8 mg oral dose is approximately 99%. Rosiglitazone plasma concentrations peak at around 1 h after dosing. Plasma concentrations 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 C_{max} (approximately 20-28%) and a delay in t_{max} (approximately 1.75 h) were observed compared to dosing in the fasting 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.

Distribution

The volume of distribution of rosiglitazone is approximately 14 l in healthy volunteers. Plasma protein binding of rosiglitazone is high (approximately 99.8%) and is not influenced by concentration or age. The protein binding of the major metabolite (a para-hydroxy-sulphate) is very high (> 99.99%).

Metabolism

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 contribution of the major metabolite (a para-hydroxy-sulphate) to

Medicinal product no longer authorised

the overall antihyperglycaemic activity of rosiglitazone has not been fully elucidated in man and it cannot be ruled out that the metabolite may contribute to the activity. However, this raises no safety concern regarding target or special populations as hepatic impairment is contraindicated and the phase III clinical studies included a considerable number of elderly patients and patients with mild to moderate renal impairment.

In vitro studies demonstrate that rosiglitazone is predominantly metabolised by CYP2C8, with a minor contribution by CYP2C9.

Since there is no significant *in vitro* inhibition of CYP1A2, 2A6, 2C19, 2D6, 2E1, 3A or 4A with rosiglitazone, there is a low probability of significant metabolism-based interactions with substances metabolised by these P450 enzymes. Rosiglitazone showed moderate inhibition of CYP2C8 (IC_{50} 18 μM) and low inhibition of CYP2C9 (IC_{50} 50 μM) *in vitro* (see section 4.5). An *in vivo* interaction study with warfarin indicated that rosiglitazone does not interact with CYP2C9 substrates *in vivo*.

Elimination

Total plasma clearance of rosiglitazone is around 3 l/h and the terminal elimination half-life of rosiglitazone is approximately 3-4 h. There is no evidence for unexpected accumulation of rosiglitazone after once or twice daily dosing. The major route of excretion is the urine with approximately two-thirds of the dose being eliminated by this route, whereas faecal elimination accounts for approximately 25% of dose. No intact active substance is excreted in urine or faeces. The terminal half-life for radioactivity was about 130 h indicating that elimination of metabolites is very slow. Accumulation of the metabolites in plasma is expected upon repeated dosing, especially that of the major metabolite (a para-hydroxy-sulphate) for which an 8-fold accumulation is anticipated.

Special populations

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.

Children and adolescents: Population pharmacokinetic analysis including 96 paediatric patients aged 10 to 18 years and weighing 35 to 178 kg suggested similar mean CL/F in children and adults. Individual CL/F in the paediatric population was in the same range as individual adult data. CL/F seemed to be independent of age, but increased with weight in the paediatric population.

Hepatic impairment: In cirrhotic patients with moderate (Child-Pugh B) hepatic impairment, unbound C_{max} and AUC were 2- and 3-fold higher than in normal subjects. The inter-subject variability was large, with a 7-fold difference in unbound AUC between patients.

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.

Metformin

Absorption

After an oral dose of metformin, t_{max} is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 μg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 μg/ml, even at maximum doses.

Medicinal product no longer authorised

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Distribution
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean V_d ranged between 63 – 276 l.

Metabolism
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination
Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3 Preclinical safety data

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
Undesirable effects observed in animal studies with possible relevance to clinical use were as follows: An increase in plasma volume accompanied by decrease in red cell parameters and increase in heart weight. Increases in liver weight, plasma ALT (dog only) and fat tissue were also observed. Similar effects have been seen with other thiazolidinediones.

In reproductive toxicity studies, administration of rosiglitazone to rats during mid-late gestation was associated with foetal death and retarded foetal development. In addition, rosiglitazone inhibited ovarian oestradiol and progesterone synthesis and lowered plasma levels of these hormones resulting in effects on oestrus/menstrual cycles and fertility (see section 4.4).

In an animal model for familial adenomatous polyposis (FAP), treatment with rosiglitazone at 200 times the pharmacologically active dose increased tumour multiplicity in the colon. The relevance of this finding is unknown. However, rosiglitazone promoted differentiation and reversal of mutagenic changes in human colon cancer cells *in vitro*. In addition, rosiglitazone was not genotoxic in a battery of *in vivo* and *in vitro* genotoxicity studies and there was no evidence of colon tumours in lifetime studies of rosiglitazone in two rodent species.

Metformin
Non-clinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Sodium starch glycollate
Hypromellose (E464)
Microcrystalline cellulose (E460)

Medicinal product no longer authorised

Lactose monohydrate
Povidone (E1201)
Magnesium stearate.

Film coat:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol
Iron oxide red (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Opaque blisters (PVC/PVdC/aluminium). Packs of 28, 56, 112, 336 (3x112) and 360 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/004-006
EU/1/03/258/016
EU/1/03/258/020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 October 2003
Date of latest renewal: 20 October 2008

10. DATE OF REVISION OF THE TEXT

Medicinal product no longer authorised

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.ema.europa.eu

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 2 mg/1000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of rosiglitazone (as rosiglitazone maleate) and 1000 mg of metformin hydrochloride (corresponding to metformin free base 780 mg).

Excipients:
Each tablet contains lactose (approximately 11 mg)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow film-coated tablets marked "gsk" on one side and "2/1000" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AVANDAMET is indicated in the treatment of type 2 diabetes mellitus patients, particularly overweight patients:

- who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone.
- in triple oral therapy with sulphonylurea in patients with insufficient glycaemic control despite dual oral therapy with their maximally tolerated dose of metformin and a sulphonylurea (see section 4.4).

4.2 Posology and method of administration

For the different dosage regimens, AVANDAMET is available in appropriate strengths.

The usual starting dose of AVANDAMET is 4 mg/day rosiglitazone plus 2000 mg/day metformin hydrochloride.

Rosiglitazone can be increased to 8 mg/day after 8 weeks if greater glycaemic control is required. The maximum recommended daily dose of AVANDAMET is 8 mg rosiglitazone plus 2000 mg metformin hydrochloride.

The total daily dose of AVANDAMET should be given in two divided doses.

Dose titration with rosiglitazone (added to the optimal dose of metformin) may be considered before the patient is switched to AVANDAMET.

When clinically appropriate, direct change from metformin monotherapy to AVANDAMET may be considered.

Taking AVANDAMET with or just after food may reduce gastrointestinal symptoms associated with metformin.

Medicinal product no longer authorised

Triple oral therapy (rosiglitazone, metformin and sulphonylurea) (see section 4.4)

- Patients on metformin and sulphonylurea: when appropriate AVANDAMET may be initiated at 4 mg/day rosiglitazone with the dose of metformin substituting that already being taken. An increase in the rosiglitazone component to 8 mg/day should be undertaken cautiously following appropriate clinical evaluation to assess the patient's risk of developing adverse reactions relating to fluid retention (see sections 4.4 and 4.8).
- Patients established on triple oral therapy: when appropriate, AVANDAMET may substitute rosiglitazone and metformin doses already being taken.

Where appropriate, AVANDAMET may be used to substitute concomitant rosiglitazone and metformin in existing dual or triple oral therapy to simplify treatment.

Elderly

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking AVANDAMET should have their renal function monitored regularly (see sections 4.3 and 4.4).

Patients with renal impairment

AVANDAMET should not be used in patients with renal failure or renal dysfunction e.g. serum creatinine levels > 135 µmol/l in males and > 110 µmol/l in females and/or creatinine clearance < 70 ml/min (see sections 4.3 and 4.4).

Children and adolescents

AVANDAMET is not recommended for use in children and adolescents below 18 years of age as there are no data available on its safety and efficacy in this age group (see sections 5.1 and 5.2).

4.3 Contraindications

AVANDAMET is contraindicated in patients with:

- hypersensitivity to rosiglitazone, metformin hydrochloride or to any of the excipients
- cardiac failure or history of cardiac failure (New York Heart Association (NYHA) stages I to IV)
- an Acute Coronary Syndrome (unstable angina, NSTEMI and STEMI) (see section 4.4)
- acute or chronic disease which may cause tissue hypoxia such as:
    - cardiac or respiratory failure
    - recent myocardial infarction
    - shock
- hepatic impairment
- acute alcohol intoxication, alcoholism (see section 4.4)
- diabetic ketoacidosis or diabetic pre-coma
- renal failure or renal dysfunction e.g. serum creatinine levels > 135 µmol/l in males and > 110 µmol/l in females and/or creatinine clearance < 70 ml/min (see section 4.4)
- acute conditions with the potential to alter renal function such as:
    - dehydration
    - severe infection
    - shock
    - intravascular administration of iodinated contrast agents (see section 4.4)
- lactation.

4.4 Special warnings and precautions for use

Lactic acidosis

Lactic acidosis is a very rare, but serious, metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis,

Medicinal product no longer authorised

prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia.

Diagnosis:
Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/l and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately (see section 4.9).

Renal function
As metformin is excreted by the kidney, serum creatinine concentrations should be determined regularly:
- at least once a year in patients with normal renal function
- at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly patients.

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with an NSAID.

Fluid retention and cardiac failure
Thiazolidinediones can cause fluid retention which may exacerbate or precipitate signs or symptoms of congestive heart failure. Rosiglitazone can cause dose-dependent fluid retention. The possible contribution of fluid retention to weight gain should be individually assessed as rapid and excessive weight gain has been reported very rarely as a sign of fluid retention. All patients, particularly those receiving concurrent insulin but also sulphonylurea therapy, those at risk for heart failure, and those with reduced cardiac reserve, should be monitored for signs and symptoms of adverse reactions relating to fluid retention, including weight gain and heart failure. AVANDAMET must be discontinued if any deterioration in cardiac status occurs.

The use of AVANDAMET in combination with a sulphonylurea or insulin may be associated with increased risks of fluid retention and heart failure (see section 4.8). The decision to initiate AVANDAMET in combination with a sulphonylurea should include consideration of alternative therapies. Increased monitoring of the patient is recommended if AVANDAMET is used in combination particularly with insulin but also with a sulphonylurea.

Heart failure was also reported more frequently in patients with a history of heart failure; oedema and heart failure was also reported more frequently in elderly patients and in patients with mild or moderate renal failure. Caution should be exercised in patients over 75 years because of the limited experience in this patient group. Since NSAIDs, insulin and rosiglitazone are all associated with fluid retention, concomitant administration may increase the risk of oedema.

Combination with insulin
An increased incidence of cardiac failure has been observed in clinical trials when rosiglitazone is 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. Insulin should only be added to established rosiglitazone therapy in exceptional cases and under close supervision.

Myocardial Ischaemia
A retrospective analysis of data from 42 pooled short-term clinical studies indicated that treatment with rosiglitazone may be associated with an increased risk of myocardial ischaemic events. However, in their entirety the available data on the risk of cardiac ischaemia are inconclusive (see section 4.8). There are limited clinical trial data in patients with ischaemic heart disease and/or peripheral arterial disease. Therefore, as a precaution, the use of rosiglitazone is not recommended in these patients, particularly those with myocardial ischaemic symptoms.

Medicinal product no longer authorised

Acute Coronary Syndrome (ACS)
Patients experiencing an ACS have not been studied in rosiglitazone controlled clinical trials. In view of the potential for development of heart failure in these patients, rosiglitazone should therefore not be initiated in patients having an acute coronary event and it should be discontinued during the acute phase (see section 4.3).

Monitoring of liver function
There have been rare reports of hepatocellular dysfunction during post-marketing experience with rosiglitazone (see section 4.8). There is limited experience with rosiglitazone in patients with elevated liver enzymes (ALT > 2.5 times the upper limit of normal). Therefore, liver enzymes should be checked prior to the initiation of therapy with AVANDAMET in all patients and periodically thereafter based on clinical judgement. Therapy with AVANDAMET should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 times the upper limit of normal) or with any other evidence of liver disease. If ALT levels are increased to > 3 times the upper limit of normal during AVANDAMET therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 times the upper limit of normal, therapy 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, therapy should be discontinued.

Eye disorders
Post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with thiazolidinediones, including rosiglitazone. Many of these patients reported concurrent peripheral oedema. It is unclear whether or not there is a direct association between rosiglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity and appropriate ophthalmologic referral should be considered.

Weight gain
In clinical trials with rosiglitazone there was evidence of dose-related weight gain, which was greater when used in combination with insulin. Therefore weight should be closely monitored, given that it may be attributable to fluid retention, which may be associated with cardiac failure.

Anaemia
Rosiglitazone treatment is associated with a dose-related reduction of haemoglobin levels. In patients with low haemoglobin levels before initiating therapy, there is an increased risk of anaemia during treatment with AVANDAMET.

Hypoglycaemia
Patients receiving AVANDAMET in combination with a sulphonylurea or insulin may be at risk for dose-related hypoglycaemia. Increased monitoring of the patient and a reduction in the dose of the concomitant agent may be necessary.

Surgery
As AVANDAMET contains metformin hydrochloride, the treatment should be discontinued 48 hours before elective surgery with general anaesthesia and should not usually be resumed earlier than 48 hours afterwards.

Administration of iodinated contrast agent
The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure. Therefore, due to the metformin active substance, AVANDAMET should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.5).

Bone disorders

Medicinal product no longer authorised

Long-term studies show an increased incidence of bone fractures in patients, particularly female patients, taking rosiglitazone (see section 4.8). The majority of the fractures have occurred in the upper limbs and distal lower limbs. In females, this increased incidence was noted after the first year of treatment and persisted during long-term treatment. The risk of fracture should be considered in the care of patients, especially female patients, treated with rosiglitazone.

Other precautions
Premenopausal women have received rosiglitazone during clinical studies. Although hormonal imbalance has been seen in preclinical studies (see section 5.3), no significant undesirable effects associated with menstrual disorders have been observed. As a consequence of improving insulin sensitivity, resumption of ovulation may occur in patients who are anovulatory due to insulin resistance. Patients should be aware of the risk of pregnancy (see section 4.6).

AVANDAMET should be used with caution during concomitant administration of CYP2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin), due to the effect on rosiglitazone pharmacokinetics (see section 4.5). Furthermore, AVANDAMET should be used with caution during concomitant administration of cationic medicinal products that are eliminated by renal tubular secretion (e.g. cimetidine) due to the effect on metformin pharmacokinetics (see section 4.5). Glycaemic control should be monitored closely. AVANDAMET dose adjustment within the recommended posology or changes in diabetic treatment should be considered.

All patients should continue their diet with regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
The usual laboratory tests for diabetes monitoring should be performed regularly.

AVANDAMET tablets contain lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for AVANDAMET, however the concomitant use of the active substances in patients in clinical studies and in widespread clinical use has not resulted in any unexpected interactions. The following statements reflect the information available on the individual active substances (rosiglitazone and metformin).

There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic insufficiency) due to the metformin active substance of AVANDAMET (see section 4.4). Avoid consumption of alcohol and medicinal products containing alcohol.
Cationic medicinal products that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and C_{max} by 81%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered (see section 4.4).

In vitro studies demonstrate that rosiglitazone is predominantly metabolised by CYP2C8, with CYP2C9 as only a minor pathway.

Co-administration of rosiglitazone with gemfibrozil (an inhibitor of CYP2C8) resulted in a twofold increase in rosiglitazone plasma concentrations. Since there is a potential for an increase in the risk of dose-related adverse reactions, a decrease in rosiglitazone dose may be needed. Close monitoring of glycaemic control should be considered (see section 4.4).

Medicinal product no longer authorised

Co-administration of rosiglitazone with rifampicin (an inducer of CYP2C8) resulted in a 66% decrease in rosiglitazone plasma concentrations. It cannot be excluded that other inducers (e.g. phenytoin, carbamazepine, phenobarbital, St John's wort) may also affect rosiglitazone exposure. The rosiglitazone dose may need to be increased. Close monitoring of glycaemic control should be considered (see section 4.4).

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

Concomitant administration of rosiglitazone with the oral antihyperglycaemic agents glibenclamide and acarbose did not result in any clinically relevant pharmacokinetic interactions.

No clinically relevant interactions with digoxin, the CYP2C9 substrate warfarin, the CYP3A4 substrates nifedipine, ethinylestradiol or norethindrone were observed after co-administration with rosiglitazone.

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.

Combination requiring precautions for use
Glucocorticoids (given by systemic and local routes) beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment. If necessary, the dosage of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.
ACE-inhibitors may decrease the blood glucose levels. If necessary, the dosage of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

4.6 Pregnancy and lactation

For AVANDAMET no preclinical or clinical data on exposed pregnancies or lactation are available.

Rosiglitazone has been reported to cross the human placenta and to be detectable in foetal tissues. There are no adequate data from the use of rosiglitazone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Therefore, AVANDAMET should not be used during pregnancy. If a patient wishes to become pregnant or if pregnancy occurs, treatment with AVANDAMET should be discontinued unless the expected benefit to the mother outweighs the potential risk to the foetus.
Both rosiglitazone and metformin have been detected in the milk of experimental animals. It is not known whether breast-feeding will lead to exposure of the infant to the medicinal product. AVANDAMET must therefore not be used in women who are breast-feeding (see section 4.3).

4.7 Effects on ability to drive and use machines

AVANDAMET has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are presented below for each of the component parts of AVANDAMET. An adverse reaction is only presented for the fixed dose combination if it has not been seen in one of the component parts of AVANDAMET or if it occurred at a higher frequency than that listed for a component part.

Medicinal product no longer authorised

Adverse reactions for each treatment regimen are presented below by system organ class and absolute frequency. For dose-related adverse reactions the frequency category reflects the higher dose of rosiglitazone. Frequency categories do not account for other factors including varying study duration, pre-existing conditions and baseline patient characteristics. Adverse reaction frequency categories assigned based on clinical trial experience may not reflect the frequency of adverse events occurring during normal clinical practice. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000 including isolated reports).

AVANDAMET

Data from double-blind studies confirm that the safety profile of concomitant rosiglitazone and metformin is similar to that of the combined adverse reaction profile for the two medicinal products. Data with AVANDAMET is also consistent with this combined adverse reaction profile.

Clinical trial data (addition of insulin to established AVANDAMET therapy)
In a single study (n=322) where insulin was added to patients established on AVANDAMET, no new adverse events were observed in excess of those already defined for either AVANDAMET or rosiglitazone combination therapies.

However, the risk of both fluid related adverse events and hypoglycaemia are increased when AVANDAMET is used in combination with insulin.

Rosiglitazone

Clinical trial data
Adverse reactions for each treatment regimen are presented below by system organ class and absolute frequency. For dose-related adverse reactions the frequency category reflects the higher dose of rosiglitazone. Frequency categories do not account for other factors including varying study duration, pre-existing conditions and baseline patient characteristics.

Table 1 lists adverse reactions identified from an overview of clinical trials involving over 5,000 rosiglitazone-treated patients. Within each system organ class, adverse reactions are presented in the table by decreasing frequency for the rosiglitazone monotherapy treatment regimen. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Medicinal product no longer authorised

Table 1. The frequency of adverse reactions identified from clinical trial data with rosiglitazone

Adverse reaction	Frequency of adverse reaction by treatment regimen		
	Rosiglitazone monotherapy	**Rosiglitazone with metformin**	**Rosiglitazone with metformin and sulphonylurea**
Blood and the lymphatic system disorders			
anaemia	Common	Common	Common
granulocytopaenia			Common
Metabolism and nutrition disorders			
hypercholesterolaemia[1]	Common	Common	Common
hypertriglyceridaemia	Common		
hyperlipaemia	Common	Common	Common
weight increase	Common	Common	Common
increased appetite	Common		
hypoglycaemia		Common	Very common
Nervous system disorders			
dizziness*		Common	
headache*			Common
Cardiac disorders			
cardiac failure[2]		Common	Common
cardiac ischaemia[3]*	Common	Common	Common
Gastrointestinal disorders			
constipation	Common	Common	Common
Musculoskeletal and connective tissue disorders			
bone fractures[4]	Common	Common	
myalgia*			Common
General disorders and administration site conditions			
oedema	Common	Common	Very common

*The frequency category for the background incidence of these events, as taken from placebo group data from clinical trials, is 'common'.

[1] Hypercholesterolaemia was reported in up to 5.3% of patients treated with rosiglitazone (monotherapy, dual or triple oral therapy). The elevated total cholesterol levels were associated with an increase in both LDLc and HDLc, but the ratio of total cholesterol: HDLc was unchanged or improved in long term studies. Overall, these increases were generally mild to moderate and usually did not require discontinuation of treatment.

[2] An increased incidence of heart failure has been observed when rosiglitazone was added to treatment regimens with a sulphonylurea (either as dual or triple therapy), and appeared higher with 8 mg rosiglitazone compared to 4 mg rosiglitazone (total daily dose). The incidence of heart failure on triple oral therapy was 1.4% in the main double blind study, compared to 0.4% for metformin plus sulphonylurea dual therapy. The incidence of heart failure in combination with insulin (rosiglitazone added to established insulin therapy) was 2.4%, compared to insulin alone, 1.1%.

Medicinal product no longer authorised

In a placebo-controlled one-year trial in patients with congestive heart failure NYHA class I-II, worsening or possible worsening of heart failure occurred in 6.4% of patients treated with rosiglitazone, compared with 3.5% on placebo.

[3] In a retrospective analysis of data from 42 pooled short-term clinical studies, the overall incidence of events typically associated with cardiac ischaemia was higher for rosiglitazone containing regimens, 2.00% versus combined active and placebo comparators, 1.53% [hazard ratio (HR) 1.30 (95% confidence interval (CI) 1.004 - 1.69)]. This risk was increased when rosiglitazone was added to established insulin and in patients receiving nitrates for known ischaemic heart disease. In an update to this retrospective analysis that included 10 further studies that met the criteria for inclusion, but were not available at the time of the original analysis, the overall incidence of events typically associated with cardiac ischaemia was not statistically different for rosiglitazone containing regimens, 2.21% versus combined active and placebo comparators, 2.08% [HR 1.098 (95% CI 0.809 - 1.354)]. In a prospective cardiovascular outcomes study (mean follow-up 5.5 years) the primary endpoint events of cardiovascular death or hospitalisation were similar between rosiglitazone and active comparators [HR 0.99 (95% CI 0.85 - 1.16)]. Two other long-term prospective randomised controlled clinical trials (9,620 patients, study duration >3 years in each study), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded the potential risk of cardiac ischaemia. In their entirety, the available data on the risk of cardiac ischaemia are inconclusive.

[4] Long-term studies show an increased incidence of bone fracture in patients, particularly female patients, taking rosiglitazone. In a monotherapy study, the incidence in females for rosiglitazone was 9.3% (2.7 patients per 100 patient years) vs 5.1% (1.5 patients per 100 patient years) for metformin or 3.5% (1.3 patients per 100 patient years) for glibenclamide. In another long-term study, there was an increased incidence of bone fracture for subjects in the combined rosiglitazone group compared to active control [8.3% vs 5.3%, Risk ratio 1.57 (95% CI 1.26 - 1.97)]. The risk of fracture appeared to be higher in females relative to control [11.5% vs 6.3%, Risk ratio 1.82 (95% CI 1.37 - 2.41)], than in males relative to control [5.3% vs 4.3%, Risk ratio 1.23 (95% CI 0.85 - 1.77)]. Additional data are necessary to determine whether there is an increased risk of fracture in males after a longer period of follow-up. The majority of the fractures were reported in the upper limbs and distal lower limbs (see section 4.4).

In double-blind clinical trials 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/sulphonylureas). The incidence of all adverse events relating to liver and biliary systems was <1.5% in any treatment group and similar to placebo.

Post-marketing data

In addition to the adverse reactions identified from clinical trial data, the adverse reactions presented in Table 2 have been identified in post approval use of rosiglitazone.

Medicinal product no longer authorised

Table 2. The frequency of adverse reactions identified from post-marketing data with rosiglitazone

Adverse reaction	**Frequency**
Metabolism and nutrition disorders	
rapid and excessive weight gain	Very rare
Immune system disorders (see Skin and subcutaneous tissue disorders)	
anaphylactic reaction	Very rare
Eye disorders	
macular oedema	Rare
Cardiac disorders	
congestive heart failure/pulmonary oedema	Rare
Hepatobiliary disorders	
hepatic dysfunction, primarily evidenced by elevated hepatic enzymes[5]	Rare
Skin and subcutaneous tissue disorders (see Immune system disorders)	
angioedema	Very rare
skin reactions (e.g. urticaria, pruritis, rash)	Very rare

[5] Rare cases of elevated liver enzymes and hepatocellular dysfunction have been reported. In very rare cases, a fatal outcome has been reported.

Metformin

Clinical Trial Data and Post-marketing data

Table 3 presents adverse reactions by system organ class and by frequency category. Frequency categories are based on information available from metformin Summary of Product Characteristics available in the EU.

Medicinal product no longer authorised

Table 3. The frequency of metformin adverse reactions identified from clinical trial and post-marketing data

Adverse reaction	Frequency
Gastrointestinal disorders	
gastrointestinal symptoms[6]	Very common
Metabolism and nutrition disorders	
lactic acidosis	Very rare
vitamin B12 deficiency[7]	Very rare
Nervous system disorders	
metallic taste	Common
Hepatobiliary disorders	
liver function disorders	Very rare
hepatitis	Very rare
Skin and subcutaneous disorders	
urticaria	Very rare
erythema	Very rare
pruritis	Very rare

[6] Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

[7] Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g. megaloblastic anaemia).

4.9 Overdose

No data are available with regard to overdose of AVANDAMET.

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

A large overdose of metformin (or coexisting risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital.

In the event of an overdose, it is recommended that appropriate supportive treatment is 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of oral blood glucose lowering medicinal products, ATC code: A10BD03

AVANDAMET combines two antihyperglycaemic agents with complimentary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: rosiglitazone maleate, a member of the

Medicinal product no longer authorised

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.

Rosiglitazone
Rosiglitazone is a selective agonist at the PPARγ (peroxisome proliferator activated receptor gamma) nuclear receptor and is a member of the thiazolidinedione class of antihyperglycaemic agents. It reduces glycaemia by reducing insulin resistance at adipose tissue, skeletal muscle and liver.

The antihyperglycaemic activity of rosiglitazone has been demonstrated in a number of animal 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 animal models of type 2 diabetes. Rosiglitazone did not stimulate pancreatic insulin secretion or induce hypoglycaemia in rats and mice. The major metabolite (a para-hydroxy-sulphate) with high affinity to the soluble human PPARγ, exhibited relatively high potency in a glucose tolerance assay in obese mice. The clinical relevance of this observation has not been fully elucidated.

In clinical trials, the glucose lowering effects observed with rosiglitazone are gradual in onset with near maximal reductions in fasting plasma glucose (FPG) evident following approximately 8 weeks of therapy. The improved glycaemic control is associated with reductions in both fasting and post-prandial glucose.

Rosiglitazone was associated with increases in weight. In mechanistic studies, the weight increase was predominantly shown to be due to increased subcutaneous fat with decreased visceral and intra-hepatic fat.

Consistent with the mechanism of action, rosiglitazone in combination with metformin reduced insulin resistance and improved pancreatic ß-cell function. Improved glycaemic control was also associated with significant decreases in free fatty acids. As a consequence of different but complementary mechanisms of action, combination therapy of rosiglitazone with metformin resulted in additive effects on glycaemic control in type 2 diabetic patients.

In studies with a maximal duration of three years, rosiglitazone given once or twice daily in dual oral therapy with metformin produced a sustained improvement in glycaemic control (FPG and HbA1c). A more pronounced glucose-lowering effect was observed in obese patients. An outcome study has not been completed with rosiglitazone, therefore the long-term benefits associated with improved glycaemic control of rosiglitazone have not been demonstrated.

An active controlled clinical trial (rosiglitazone up to 8 mg daily or metformin up to 2,000 mg daily) of 24 weeks duration was performed in 197 children (10-17 years of age) with type 2 diabetes. Improvement in HbA1c from baseline achieved statistical significance only in the metformin group. Rosiglitazone failed to demonstrate non-inferiority to metformin. Following rosiglitazone treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. No long-term efficacy and safety data are available in paediatric patients.

ADOPT (A Diabetes Outcome Progression Trial) was a multicentre, double-blind, controlled trial with a treatment duration of 4-6 years (median duration of 4 years), in which rosiglitazone at doses of 4 to 8 mg/day was compared to metformin (500 mg to 2000 mg/day) and glibenclamide (2.5 to 15 mg/day) in 4351 drug naive subjects recently diagnosed (≤3 years) with type 2 diabetes. Rosiglitazone treatment significantly reduced the risk of reaching monotherapy failure (FPG>10.0 mmol/L) by 63% relative to glibenclamide (HR 0.37, CI 0.30-0.45) and by 32% relative to metformin (HR 0.68, CI 0.55-0.85) during the course of the study (up to 72 months of treatment). This translates to a cumulative incidence of treatment failure of 10.3% for rosiglitazone, 14.8% for metformin and 23.3% for glibenclamide treated patients. Overall, 43%, 47% and 42% of subjects in the rosiglitazone, glibenclamide and metformin groups respectively withdrew due to reasons other than monotherapy failure. The impact of these findings on disease progression or on microvascular or macrovascular outcomes has not been determined (see section 4.8). In this study, the adverse events observed were

Medicinal product no longer authorised

consistent with the known adverse event profile for each of the treatments, including continuing weight gain with rosiglitazone. An additional observation of an increased incidence of bone fractures was seen in women with rosiglitazone (see sections 4.4 and 4.8).

The RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) trial was a large (4,447 subjects), open-label, prospective, controlled study (mean follow-up 5.5 years) in which patients with type 2 diabetes inadequately controlled with metformin or sulphonylurea were randomised to add-on rosiglitazone or metformin or sulphonylurea. The mean duration of diabetes in these patients was approximately 7 years. The adjudicated primary endpoint was cardiovascular hospitalisation (which included hospitalisations for heart failure) or cardiovascular death. Mean doses at the end of randomised treatment are shown in the following table:

Randomised Treatment†	**Mean (SD) dose at end of randomised treatment**
Rosiglitazone (either SU or metformin)	6.7 (1.9) mg
Sulphonylurea (background metformin)	
Glimepiride*	3.6 (1.8) mg
Metformin (background sulphonylurea)	1995.5 (682.6) mg

*Similar relative effective doses (i.e approximately half maximal dose) for other sulphonylureas (glibenclamide and glicazide).
† Patients who took designated treatment as randomised in combination with the correct background treatment and with evaluable data.

No difference in the number of adjudicated primary endpoint events for rosiglitazone (321/2220) versus active control (323/2227) (HR 0.99, CI 0.85-1.16) was observed, meeting the pre-defined non-inferiority criterion of 1.20 (non-inferiority p = 0.02). HR and CI for key secondary endpoints were: all-cause death (HR 0.86, CI 0.68-1.08), MACE (Major Adverse Cardiac Events - cardiovascular death, acute myocardial infarction, stroke) (HR 0.93, CI 0.74-1.15), cardiovascular death (HR 0.84, CI 0.59-1.18), acute myocardial infarction (HR 1.14, CI 0.80-1.63) and stroke (HR 0.72, CI 0.49-1.06). In a sub-study at 18 months, add-on rosiglitazone dual therapy was non-inferior to the combination of sulphonylurea plus metformin for lowering HbA1c. In the final analysis at 5 years, an adjusted mean reduction from baseline in HbA1c of 0.14% for patients on rosiglitazone added to metformin versus an increase of 0.17% for patients taking sulphonylurea added to metformin was seen during treatment with randomised dual-combination therapy ($p<0.0001$ for treatment difference). An adjusted mean reduction in HbA1c of 0.24% was seen for patients taking rosiglitazone added to sulphonylurea, versus a reduction in HbA1c of 0.10% for patients taking metformin added to sulphonylurea, ($p=0.0083$ for treatment difference). There was a significant increase in heart failure (fatal and non-fatal) (HR 2.10, CI 1.35-3.27) and bone fractures (Risk Ratio 1.57, CI 1.26-1.97) in rosiglitazone-containing treatments compared to active control (see sections 4.4 and 4.8). A total of 564 patients withdrew from cardiovascular follow-up, which accounted for 12.3% of rosiglitazone patients and 13% of control patients; representing 7.2% of patient-years lost for cardiovascular events follow-up and 2.0% of patient-years lost for all cause mortality follow-up.

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 three 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).

Medicinal product no longer authorised

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, LDLc and triglyceride levels.

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034
- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021)
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years (p=0.01).

5.2 Pharmacokinetic properties

AVANDAMET

Absorption

No statistically significant difference was observed between the absorption characteristics of rosiglitazone and metformin from the AVANDAMET tablet and those obtained from rosiglitazone maleate and metformin hydrochloride tablets, respectively.

Food had no effect on the AUC of rosiglitazone or metformin when AVANDAMET was administered to healthy volunteers. In the fed state, C_{max} was lower (22% rosiglitazone and 15% metformin) and t_{max} delayed (by approximately 1.5 h rosiglitazone and 0.5 h metformin). This food-effect is not considered clinically significant.

The following statements reflect the pharmacokinetic properties of the individual active substances of AVANDAMET.

Rosiglitazone

Absorption

Absolute bioavailability of rosiglitazone following both a 4 and an 8 mg oral dose is approximately 99%. Rosiglitazone plasma concentrations peak at around 1 h after dosing. Plasma concentrations 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 C_{max} (approximately 20-28%) and a delay in t_{max} (approximately 1.75 h) were observed compared to dosing in the fasting 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.

Distribution

The volume of distribution of rosiglitazone is approximately 14 l in healthy volunteers. Plasma protein binding of rosiglitazone is high (approximately 99.8%) and is not influenced by concentration or age. The protein binding of the major metabolite (a para-hydroxy-sulphate) is very high (> 99.99%).

Metabolism

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 contribution of the major metabolite (a para-hydroxy-sulphate) to

Medicinal product no longer authorised

the overall antihyperglycaemic activity of rosiglitazone has not been fully elucidated in man and it cannot be ruled out that the metabolite may contribute to the activity. However, this raises no safety concern regarding target or special populations as hepatic impairment is contraindicated and the phase III clinical studies included a considerable number of elderly patients and patients with mild to moderate renal impairment.

In vitro studies demonstrate that rosiglitazone is predominantly metabolised by CYP2C8, with a minor contribution by CYP2C9.

Since there is no significant *in vitro* inhibition of CYP1A2, 2A6, 2C19, 2D6, 2E1, 3A or 4A with rosiglitazone, there is a low probability of significant metabolism-based interactions with substances metabolised by these P450 enzymes. Rosiglitazone showed moderate inhibition of CYP2C8 (IC_{50} 18 μM) and low inhibition of CYP2C9 (IC_{50} 50 μM) *in vitro* (see section 4.5). An *in vivo* interaction study with warfarin indicated that rosiglitazone does not interact with CYP2C9 substrates *in vivo*.

Elimination

Total plasma clearance of rosiglitazone is around 3 l/h and the terminal elimination half-life of rosiglitazone is approximately 3-4 h. There is no evidence for unexpected accumulation of rosiglitazone after once or twice daily dosing. The major route of excretion is the urine with approximately two-thirds of the dose being eliminated by this route, whereas faecal elimination accounts for approximately 25% of dose. No intact active substance is excreted in urine or faeces. The terminal half-life for radioactivity was about 130 h indicating that elimination of metabolites is very slow. Accumulation of the metabolites in plasma is expected upon repeated dosing, especially that of the major metabolite (a para-hydroxy-sulphate) for which an 8-fold accumulation is anticipated.

Special populations

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.

Children and adolescents: Population pharmacokinetic analysis including 96 paediatric patients aged 10 to 18 years and weighing 35 to 178 kg suggested similar mean CL/F in children and adults. Individual CL/F in the paediatric population was in the same range as individual adult data. CL/F seemed to be independent of age, but increased with weight in the paediatric population.

Hepatic impairment: In cirrhotic patients with moderate (Child-Pugh B) hepatic impairment, unbound C_{max} and AUC were 2- and 3-fold higher than in normal subjects. The inter-subject variability was large, with a 7-fold difference in unbound AUC between patients.

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.

Metformin

Absorption

After an oral dose of metformin, t_{max} is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 μg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 μg/ml, even at maximum doses.

Medicinal product no longer authorised

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Distribution
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean V_d ranged between 63 – 276 l.

Metabolism
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination
Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3 Preclinical safety data

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
Undesirable effects observed in animal studies with possible relevance to clinical use were as follows: An increase in plasma volume accompanied by decrease in red cell parameters and increase in heart weight. Increases in liver weight, plasma ALT (dog only) and fat tissue were also observed. Similar effects have been seen with other thiazolidinediones.

In reproductive toxicity studies, administration of rosiglitazone to rats during mid-late gestation was associated with foetal death and retarded foetal development. In addition, rosiglitazone inhibited ovarian oestradiol and progesterone synthesis and lowered plasma levels of these hormones resulting in effects on oestrus/menstrual cycles and fertility (see section 4.4).

In an animal model for familial adenomatous polyposis (FAP), treatment with rosiglitazone at 200 times the pharmacologically active dose increased tumour multiplicity in the colon. The relevance of this finding is unknown. However, rosiglitazone promoted differentiation and reversal of mutagenic changes in human colon cancer cells *in vitro*. In addition, rosiglitazone was not genotoxic in a battery of *in vivo* and *in vitro* genotoxicity studies and there was no evidence of colon tumours in lifetime studies of rosiglitazone in two rodent species.

Metformin
Non-clinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Sodium starch glycollate
Hypromellose (E464)
Microcrystalline cellulose (E460)

Medicinal product no longer authorised

Lactose monohydrate
Povidone (E1201)
Magnesium stearate.

Film coat:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol
Iron oxide yellow (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Opaque blisters (PVC/PVdC/aluminium). Packs of 14, 28, 56, 112 (2x56), 168 (3x56) and 180 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/007-009
EU/1/03/258/013
EU/1/03/258/017
EU/1/03/258/021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 October 2003
Date of latest renewal: 20 October 2008

10. DATE OF REVISION OF THE TEXT

Medicinal product no longer authorised

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.ema.europa.eu

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 4 mg/1000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4 mg of rosiglitazone (as rosiglitazone maleate) and 1000 mg of metformin hydrochloride (corresponding to metformin free base 780 mg).

Excipients:
Each tablet contains lactose (approximately 23 mg)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink film-coated tablets marked "gsk" on one side and "4/1000" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AVANDAMET is indicated in the treatment of type 2 diabetes mellitus patients, particularly overweight patients:

- who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone.
- in triple oral therapy with sulphonylurea in patients with insufficient glycaemic control despite dual oral therapy with their maximally tolerated dose of metformin and a sulphonylurea (see section 4.4).

4.2 Posology and method of administration

For the different dosage regimens, AVANDAMET is available in appropriate strengths.

The usual starting dose of AVANDAMET is 4 mg/day rosiglitazone plus 2000 mg/day metformin hydrochloride.

Rosiglitazone can be increased to 8 mg/day after 8 weeks if greater glycaemic control is required. The maximum recommended daily dose of AVANDAMET is 8 mg rosiglitazone plus 2000 mg metformin hydrochloride.

The total daily dose of AVANDAMET should be given in two divided doses.

Dose titration with rosiglitazone (added to the optimal dose of metformin) may be considered before the patient is switched to AVANDAMET.

When clinically appropriate, direct change from metformin monotherapy to AVANDAMET may be considered.

Taking AVANDAMET with or just after food may reduce gastrointestinal symptoms associated with metformin.

Medicinal product no longer authorised

Triple oral therapy (rosiglitazone, metformin and sulphonylurea) (see section 4.4)

- Patients on metformin and sulphonylurea: when appropriate AVANDAMET may be initiated at 4 mg/day rosiglitazone with the dose of metformin substituting that already being taken. An increase in the rosiglitazone component to 8 mg/day should be undertaken cautiously following appropriate clinical evaluation to assess the patient's risk of developing adverse reactions relating to fluid retention (see sections 4.4 and 4.8).
- Patients established on triple oral therapy: when appropriate, AVANDAMET may substitute rosiglitazone and metformin doses already being taken.

Where appropriate, AVANDAMET may be used to substitute concomitant rosiglitazone and metformin in existing dual or triple oral therapy to simplify treatment.

Elderly

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking AVANDAMET should have their renal function monitored regularly (see sections 4.3 and 4.4).

Patients with renal impairment

AVANDAMET should not be used in patients with renal failure or renal dysfunction e.g. serum creatinine levels > 135 µmol/l in males and > 110 µmol/l in females and/or creatinine clearance < 70 ml/min (see sections 4.3 and 4.4).

Children and adolescents

AVANDAMET is not recommended for use in children and adolescents below 18 years of age as there are no data available on its safety and efficacy in this age group (see sections 5.1 and 5.2).

4.3 Contraindications

AVANDAMET is contraindicated in patients with:

- hypersensitivity to rosiglitazone, metformin hydrochloride or to any of the excipients
- cardiac failure or history of cardiac failure (New York Heart Association (NYHA) stages I to IV)
- an Acute Coronary Syndrome (unstable angina, NSTEMI and STEMI) (see section 4.4)
- acute or chronic disease which may cause tissue hypoxia such as:
    - cardiac or respiratory failure
    - recent myocardial infarction
    - shock
- hepatic impairment
- acute alcohol intoxication, alcoholism (see section 4.4)
- diabetic ketoacidosis or diabetic pre-coma
- renal failure or renal dysfunction e.g. serum creatinine levels > 135 µmol/l in males and > 110 µmol/l in females and/or creatinine clearance < 70 ml/min (see section 4.4)
- acute conditions with the potential to alter renal function such as:
    - dehydration
    - severe infection
    - shock
    - intravascular administration of iodinated contrast agents (see section 4.4)
- lactation.

4.4 Special warnings and precautions for use

Lactic acidosis

Lactic acidosis is a very rare, but serious, metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis,

Medicinal product no longer authorised

prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia.

Diagnosis:
Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/l and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately (see section 4.9).

Renal function
As metformin is excreted by the kidney, serum creatinine concentrations should be determined regularly:
- at least once a year in patients with normal renal function
- at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly patients.

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with an NSAID.

Fluid retention and cardiac failure
Thiazolidinediones can cause fluid retention which may exacerbate or precipitate signs or symptoms of congestive heart failure. Rosiglitazone can cause dose-dependent fluid retention. The possible contribution of fluid retention to weight gain should be individually assessed as rapid and excessive weight gain has been reported very rarely as a sign of fluid retention. All patients, particularly those receiving concurrent insulin but also sulphonylurea therapy, those at risk for heart failure, and those with reduced cardiac reserve, should be monitored for signs and symptoms of adverse reactions relating to fluid retention, including weight gain and heart failure. AVANDAMET must be discontinued if any deterioration in cardiac status occurs.

The use of AVANDAMET in combination with a sulphonylurea or insulin may be associated with increased risks of fluid retention and heart failure (see section 4.8). The decision to initiate AVANDAMET in combination with a sulphonylurea should include consideration of alternative therapies. Increased monitoring of the patient is recommended if AVANDAMET is used in combination particularly with insulin but also with a sulphonylurea.

Heart failure was also reported more frequently in patients with a history of heart failure; oedema and heart failure was also reported more frequently in elderly patients and in patients with mild or moderate renal failure. Caution should be exercised in patients over 75 years because of the limited experience in this patient group. Since NSAIDs, insulin and rosiglitazone are all associated with fluid retention, concomitant administration may increase the risk of oedema.

Combination with insulin
An increased incidence of cardiac failure has been observed in clinical trials when rosiglitazone is 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. Insulin should only be added to established rosiglitazone therapy in exceptional cases and under close supervision.

Myocardial Ischaemia
A retrospective analysis of data from 42 pooled short-term clinical studies indicated that treatment with rosiglitazone may be associated with an increased risk of myocardial ischaemic events. However, in their entirety the available data on the risk of cardiac ischaemia are inconclusive (see section 4.8). There are limited clinical trial data in patients with ischaemic heart disease and/or peripheral arterial disease. Therefore, as a precaution, the use of rosiglitazone is not recommended in these patients, particularly those with myocardial ischaemic symptoms.

Medicinal product no longer authorised

Acute Coronary Syndrome (ACS)
Patients experiencing an ACS have not been studied in rosiglitazone controlled clinical trials. In view of the potential for development of heart failure in these patients, rosiglitazone should therefore not be initiated in patients having an acute coronary event and it should be discontinued during the acute phase (see section 4.3).

Monitoring of liver function
There have been rare reports of hepatocellular dysfunction during post-marketing experience with rosiglitazone (see section 4.8). There is limited experience with rosiglitazone in patients with elevated liver enzymes (ALT > 2.5 times the upper limit of normal). Therefore, liver enzymes should be checked prior to the initiation of therapy with AVANDAMET in all patients and periodically thereafter based on clinical judgement. Therapy with AVANDAMET should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 times the upper limit of normal) or with any other evidence of liver disease. If ALT levels are increased to > 3 times the upper limit of normal during AVANDAMET therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 times the upper limit of normal, therapy 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, therapy should be discontinued.

Eye disorders
Post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with thiazolidinediones, including rosiglitazone. Many of these patients reported concurrent peripheral oedema. It is unclear whether or not there is a direct association between rosiglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity and appropriate ophthalmologic referral should be considered.

Weight gain
In clinical trials with rosiglitazone there was evidence of dose-related weight gain, which was greater when used in combination with insulin. Therefore weight should be closely monitored, given that it may be attributable to fluid retention, which may be associated with cardiac failure.

Anaemia
Rosiglitazone treatment is associated with a dose-related reduction of haemoglobin levels. In patients with low haemoglobin levels before initiating therapy, there is an increased risk of anaemia during treatment with AVANDAMET.

Hypoglycaemia
Patients receiving AVANDAMET in combination with a sulphonylurea or insulin may be at risk for dose-related hypoglycaemia. Increased monitoring of the patient and a reduction in the dose of the concomitant agent may be necessary.

Surgery
As AVANDAMET contains metformin hydrochloride, the treatment should be discontinued 48 hours before elective surgery with general anaesthesia and should not usually be resumed earlier than 48 hours afterwards.

Administration of iodinated contrast agent
The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure. Therefore, due to the metformin active substance, AVANDAMET should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.5).

Bone disorders

Medicinal product no longer authorised

Long-term studies show an increased incidence of bone fractures in patients, particularly female patients, taking rosiglitazone (see section 4.8). The majority of the fractures have occurred in the upper limbs and distal lower limbs. In females, this increased incidence was noted after the first year of treatment and persisted during long-term treatment. The risk of fracture should be considered in the care of patients, especially female patients, treated with rosiglitazone.

Other precautions
Premenopausal women have received rosiglitazone during clinical studies. Although hormonal imbalance has been seen in preclinical studies (see section 5.3), no significant undesirable effects associated with menstrual disorders have been observed. As a consequence of improving insulin sensitivity, resumption of ovulation may occur in patients who are anovulatory due to insulin resistance. Patients should be aware of the risk of pregnancy (see section 4.6).

AVANDAMET should be used with caution during concomitant administration of CYP2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin), due to the effect on rosiglitazone pharmacokinetics (see section 4.5). Furthermore, AVANDAMET should be used with caution during concomitant administration of cationic medicinal products that are eliminated by renal tubular secretion (e.g. cimetidine) due to the effect on metformin pharmacokinetics (see section 4.5). Glycaemic control should be monitored closely. AVANDAMET dose adjustment within the recommended posology or changes in diabetic treatment should be considered.
All patients should continue their diet with regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
The usual laboratory tests for diabetes monitoring should be performed regularly.

AVANDAMET tablets contain lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for AVANDAMET, however the concomitant use of the active substances in patients in clinical studies and in widespread clinical use has not resulted in any unexpected interactions. The following statements reflect the information available on the individual active substances (rosiglitazone and metformin).

There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic insufficiency) due to the metformin active substance of AVANDAMET (see section 4.4). Avoid consumption of alcohol and medicinal products containing alcohol.
Cationic medicinal products that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and C_{max} by 81%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered (see section 4.4).

In vitro studies demonstrate that rosiglitazone is predominantly metabolised by CYP2C8, with CYP2C9 as only a minor pathway.

Co-administration of rosiglitazone with gemfibrozil (an inhibitor of CYP2C8) resulted in a twofold increase in rosiglitazone plasma concentrations. Since there is a potential for an increase in the risk of dose-related adverse reactions, a decrease in rosiglitazone dose may be needed. Close monitoring of glycaemic control should be considered (see section 4.4).

Co-administration of rosiglitazone with rifampicin (an inducer of CYP2C8) resulted in a 66% decrease in rosiglitazone plasma concentrations. It cannot be excluded that other inducers (e.g. phenytoin,

Medicinal product no longer authorised

carbamazepine, phenobarbital, St John's wort) may also affect rosiglitazone exposure. The rosiglitazone dose may need to be increased. Close monitoring of glycaemic control should be considered (see section 4.4).

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

Concomitant administration of rosiglitazone with the oral antihyperglycaemic agents glibenclamide and acarbose did not result in any clinically relevant pharmacokinetic interactions.

No clinically relevant interactions with digoxin, the CYP2C9 substrate warfarin, the CYP3A4 substrates nifedipine, ethinylestradiol or norethindrone were observed after co-administration with rosiglitazone.

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.

Combination requiring precautions for use
Glucocorticoids (given by systemic and local routes) beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment. If necessary, the dosage of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.
ACE-inhibitors may decrease the blood glucose levels. If necessary, the dosage of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

4.6 Pregnancy and lactation

For AVANDAMET no preclinical or clinical data on exposed pregnancies or lactation are available.

Rosiglitazone has been reported to cross the human placenta and to be detectable in foetal tissues. There are no adequate data from the use of rosiglitazone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Therefore, AVANDAMET should not be used during pregnancy. If a patient wishes to become pregnant or if pregnancy occurs, treatment with AVANDAMET should be discontinued unless the expected benefit to the mother outweighs the potential risk to the foetus.

Both rosiglitazone and metformin have been detected in the milk of experimental animals. It is not known whether breast-feeding will lead to exposure of the infant to the medicinal product. AVANDAMET must therefore not be used in women who are breast-feeding (see section 4.3).

4.7 Effects on ability to drive and use machines

AVANDAMET has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are presented below for each of the component parts of AVANDAMET. An adverse reaction is only presented for the fixed dose combination if it has not been seen in one of the component parts of AVANDAMET or if it occurred at a higher frequency than that listed for a component part.

Medicinal product no longer authorised

Adverse reactions for each treatment regimen are presented below by system organ class and absolute frequency. For dose-related adverse reactions the frequency category reflects the higher dose of rosiglitazone. Frequency categories do not account for other factors including varying study duration, pre-existing conditions and baseline patient characteristics. Adverse reaction frequency categories assigned based on clinical trial experience may not reflect the frequency of adverse events occurring during normal clinical practice. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000 including isolated reports).

AVANDAMET

Data from double-blind studies confirm that the safety profile of concomitant rosiglitazone and metformin is similar to that of the combined adverse reaction profile for the two medicinal products. Data with AVANDAMET is also consistent with this combined adverse reaction profile.

Clinical trial data (addition of insulin to established AVANDAMET therapy)
In a single study (n=322) where insulin was added to patients established on AVANDAMET, no new adverse events were observed in excess of those already defined for either AVANDAMET or rosiglitazone combination therapies.

However, the risk of both fluid related adverse events and hypoglycaemia are increased when AVANDAMET is used in combination with insulin.

Rosiglitazone

Clinical trial data
Adverse reactions for each treatment regimen are presented below by system organ class and absolute frequency. For dose-related adverse reactions the frequency category reflects the higher dose of rosiglitazone. Frequency categories do not account for other factors including varying study duration, pre-existing conditions and baseline patient characteristics.

Table 1 lists adverse reactions identified from an overview of clinical trials involving over 5,000 rosiglitazone-treated patients. Within each system organ class, adverse reactions are presented in the table by decreasing frequency for the rosiglitazone monotherapy treatment regimen. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Medicinal product no longer authorised

Table 1. The frequency of adverse reactions identified from clinical trial data with rosiglitazone

Adverse reaction	Frequency of adverse reaction by treatment regimen		
	Rosiglitazone monotherapy	**Rosiglitazone with metformin**	**Rosiglitazone with metformin and sulphonylurea**
Blood and the lymphatic system disorders			
anaemia	Common	Common	Common
granulocytopaenia			Common
Metabolism and nutrition disorders			
hypercholesterolaemia[1]	Common	Common	Common
hypertriglyceridaemia	Common		
hyperlipaemia	Common	Common	Common
weight increase	Common	Common	Common
increased appetite	Common		
hypoglycaemia		Common	Very common
Nervous system disorders			
dizziness*		Common	
headache*			Common
Cardiac disorders			
cardiac failure[2]		Common	Common
cardiac ischaemia[3]*	Common	Common	Common
Gastrointestinal disorders			
constipation	Common	Common	Common
Musculoskeletal and connective tissue disorders			
bone fractures[4]	Common	Common	
myalgia*			Common
General disorders and administration site conditions			
oedema	Common	Common	Very common

*The frequency category for the background incidence of these events, as taken from placebo group data from clinical trials, is 'common'.

[1] Hypercholesterolaemia was reported in up to 5.3% of patients treated with rosiglitazone (monotherapy, dual or triple oral therapy). The elevated total cholesterol levels were associated with an increase in both LDLc and HDLc, but the ratio of total cholesterol: HDLc was unchanged or improved in long term studies. Overall, these increases were generally mild to moderate and usually did not require discontinuation of treatment.

[2] An increased incidence of heart failure has been observed when rosiglitazone was added to treatment regimens with a sulphonylurea (either as dual or triple therapy), and appeared higher with 8 mg rosiglitazone compared to 4 mg rosiglitazone (total daily dose). The incidence of heart failure on triple oral therapy was 1.4% in the main double blind study, compared to 0.4% for metformin plus sulphonylurea dual therapy. The incidence of heart failure in combination with insulin (rosiglitazone added to established insulin therapy) was 2.4%, compared to insulin alone, 1.1%.

In a placebo-controlled one-year trial in patients with congestive heart failure NYHA class I-II, worsening or possible worsening of heart failure occurred in 6.4% of patients treated with rosiglitazone, compared with 3.5% on placebo.

Medicinal product no longer authorised

[3] In a retrospective analysis of data from 42 pooled short-term clinical studies, the overall incidence of events typically associated with cardiac ischaemia was higher for rosiglitazone containing regimens, 2.00% versus combined active and placebo comparators, 1.53% [hazard ratio (HR) 1.30 (95% confidence interval (CI) 1.004 - 1.69)]. This risk was increased when rosiglitazone was added to established insulin and in patients receiving nitrates for known ischaemic heart disease. In an update to this retrospective analysis that included 10 further studies that met the criteria for inclusion, but were not available at the time of the original analysis, the overall incidence of events typically associated with cardiac ischaemia was not statistically different for rosiglitazone containing regimens, 2.21% versus combined active and placebo comparators, 2.08% [HR 1.098 (95% CI 0.809 - 1.354)]. In a prospective cardiovascular outcomes study (mean follow-up 5.5 years) the primary endpoint events of cardiovascular death or hospitalisation were similar between rosiglitazone and active comparators [HR 0.99 (95% CI 0.85 - 1.16)]. Two other long-term prospective randomised controlled clinical trials (9,620 patients, study duration >3 years in each study), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded the potential risk of cardiac ischaemia. In their entirety, the available data on the risk of cardiac ischaemia are inconclusive.

[4] Long-term studies show an increased incidence of bone fracture in patients, particularly female patients, taking rosiglitazone. In a monotherapy study, the incidence in females for rosiglitazone was 9.3% (2.7 patients per 100 patient years) vs 5.1% (1.5 patients per 100 patient years) for metformin or 3.5% (1.3 patients per 100 patient years) for glibenclamide. In another long-term study, there was an increased incidence of bone fracture for subjects in the combined rosiglitazone group compared to active control [8.3% vs 5.3%, Risk ratio 1.57 (95% CI 1.26 - 1.97)]. The risk of fracture appeared to be higher in females relative to control [11.5% vs 6.3%, Risk ratio 1.82 (95% CI 1.37 - 2.41)], than in males relative to control [5.3% vs 4.3%, Risk ratio 1.23 (95% CI 0.85 - 1.77)]. Additional data are necessary to determine whether there is an increased risk of fracture in males after a longer period of follow-up. The majority of the fractures were reported in the upper limbs and distal lower limbs (see section 4.4).

In double-blind clinical trials 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/sulphonylureas). The incidence of all adverse events relating to liver and biliary systems was <1.5% in any treatment group and similar to placebo.

Post-marketing data

In addition to the adverse reactions identified from clinical trial data, the adverse reactions presented in Table 2 have been identified in post approval use of rosiglitazone.

Medicinal product no longer authorised

Table 2. The frequency of adverse reactions identified from post-marketing data with rosiglitazone

Adverse reaction	**Frequency**
Metabolism and nutrition disorders	
rapid and excessive weight gain	Very rare
Immune system disorders (see Skin and subcutaneous tissue disorders)	
anaphylactic reaction	Very rare
Eye disorders	
macular oedema	Rare
Cardiac disorders	
congestive heart failure/pulmonary oedema	Rare
Hepatobiliary disorders	
hepatic dysfunction, primarily evidenced by elevated hepatic enzymes[5]	Rare
Skin and subcutaneous tissue disorders (see Immune system disorders)	
angioedema	Very rare
skin reaction (e.g. urticaria, pruritis, rash)	Very rare

[5] Rare cases of elevated liver enzymes and hepatocellular dysfunction have been reported. In very rare cases, a fatal outcome has been reported.

Metformin

Clinical Trial Data and Post-marketing data

Table 3 presents adverse reactions by system organ class and by frequency category. Frequency categories are based on information available from metformin Summary of Product Characteristics available in the EU.

Medicinal product no longer authorised

Table 3. The frequency of metformin adverse reactions identified from clinical trial and post-marketing data

Adverse reaction	Frequency
Gastrointestinal disorders	
gastrointestinal symptoms[6]	Very common
Metabolism and nutrition disorders	
lactic acidosis	Very rare
vitamin B12 deficiency[7]	Very rare
Nervous system disorders	
metallic taste	Common
Hepatobiliary disorders	
liver function disorders	Very rare
hepatitis	Very rare
Skin and subcutaneous disorders	
urticaria	Very rare
erythema	Very rare
pruritis	Very rare

[6] Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

[7] Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g. megaloblastic anaemia).

4.9 Overdose

No data are available with regard to overdose of AVANDAMET.

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

A large overdose of metformin (or coexisting risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital.

In the event of an overdose, it is recommended that appropriate supportive treatment is 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of oral blood glucose lowering medicinal products, ATC code: A10BD03

AVANDAMET combines two antihyperglycaemic agents with complimentary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: rosiglitazone maleate, a member of the

Medicinal product no longer authorised

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.

Rosiglitazone
Rosiglitazone is a selective agonist at the PPARγ (peroxisome proliferator activated receptor gamma) nuclear receptor and is a member of the thiazolidinedione class of antihyperglycaemic agents. It reduces glycaemia by reducing insulin resistance at adipose tissue, skeletal muscle and liver.

The antihyperglycaemic activity of rosiglitazone has been demonstrated in a number of animal 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 animal models of type 2 diabetes. Rosiglitazone did not stimulate pancreatic insulin secretion or induce hypoglycaemia in rats and mice. The major metabolite (a para-hydroxy-sulphate) with high affinity to the soluble human PPARγ, exhibited relatively high potency in a glucose tolerance assay in obese mice. The clinical relevance of this observation has not been fully elucidated.

In clinical trials, the glucose lowering effects observed with rosiglitazone are gradual in onset with near maximal reductions in fasting plasma glucose (FPG) evident following approximately 8 weeks of therapy. The improved glycaemic control is associated with reductions in both fasting and post-prandial glucose.

Rosiglitazone was associated with increases in weight. In mechanistic studies, the weight increase was predominantly shown to be due to increased subcutaneous fat with decreased visceral and intra-hepatic fat.

Consistent with the mechanism of action, rosiglitazone in combination with metformin reduced insulin resistance and improved pancreatic ß-cell function. Improved glycaemic control was also associated with significant decreases in free fatty acids. As a consequence of different but complementary mechanisms of action, combination therapy of rosiglitazone with metformin resulted in additive effects on glycaemic control in type 2 diabetic patients.

In studies with a maximal duration of three years, rosiglitazone given once or twice daily in dual oral therapy with metformin produced a sustained improvement in glycaemic control (FPG and HbA1c). A more pronounced glucose-lowering effect was observed in obese patients. An outcome study has not been completed with rosiglitazone, therefore the long-term benefits associated with improved glycaemic control of rosiglitazone have not been demonstrated.

An active controlled clinical trial (rosiglitazone up to 8 mg daily or metformin up to 2,000 mg daily) of 24 weeks duration was performed in 197 children (10-17 years of age) with type 2 diabetes. Improvement in HbA1c from baseline achieved statistical significance only in the metformin group. Rosiglitazone failed to demonstrate non-inferiority to metformin. Following rosiglitazone treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. No long-term efficacy and safety data are available in paediatric patients.

ADOPT (A Diabetes Outcome Progression Trial) was a multicentre, double-blind, controlled trial with a treatment duration of 4-6 years (median duration of 4 years), in which rosiglitazone at doses of 4 to 8 mg/day was compared to metformin (500 mg to 2000 mg/day) and glibenclamide (2.5 to 15 mg/day) in 4351 drug naive subjects recently diagnosed (≤3 years) with type 2 diabetes. Rosiglitazone treatment significantly reduced the risk of reaching monotherapy failure (FPG>10.0 mmol/L) by 63% relative to glibenclamide (HR 0.37, CI 0.30-0.45) and by 32% relative to metformin (HR 0.68, CI 0.55-0.85) during the course of the study (up to 72 months of treatment). This translates to a cumulative incidence of treatment failure of 10.3% for rosiglitazone, 14.8% for metformin and 23.3% for glibenclamide treated patients. Overall, 43%, 47% and 42% of subjects in the rosiglitazone, glibenclamide and metformin groups respectively withdrew due to reasons other than monotherapy failure. The impact of these findings on disease progression or on microvascular or macrovascular outcomes has not been determined (see section 4.8). In this study, the adverse events observed were

Medicinal product no longer authorised

consistent with the known adverse event profile for each of the treatments, including continuing weight gain with rosiglitazone. An additional observation of an increased incidence of bone fractures was seen in women with rosiglitazone (see sections 4.4 and 4.8).

The RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) trial was a large (4,447 subjects), open-label, prospective, controlled study (mean follow-up 5.5 years) in which patients with type 2 diabetes inadequately controlled with metformin or sulphonylurea were randomised to add-on rosiglitazone or metformin or sulphonylurea. The mean duration of diabetes in these patients was approximately 7 years. The adjudicated primary endpoint was cardiovascular hospitalisation (which included hospitalisations for heart failure) or cardiovascular death. Mean doses at the end of randomised treatment are shown in the following table:

Randomised Treatment†	**Mean (SD) dose at end of randomised treatment**
Rosiglitazone (either SU or metformin)	6.7 (1.9) mg
Sulphonylurea (background metformin)	
Glimepiride*	3.6 (1.8) mg
Metformin (background sulphonylurea)	1995.5 (682.6) mg

*Similar relative effective doses (i.e approximately half maximal dose) for other sulphonylureas (glibenclamide and glicazide).
† Patients who took designated treatment as randomised in combination with the correct background treatment and with evaluable data.

No difference in the number of adjudicated primary endpoint events for rosiglitazone (321/2220) versus active control (323/2227) (HR 0.99, CI 0.85-1.16) was observed, meeting the pre-defined non-inferiority criterion of 1.20 (non-inferiority p = 0.02). HR and CI for key secondary endpoints were: all-cause death (HR 0.86, CI 0.68-1.08), MACE (Major Adverse Cardiac Events - cardiovascular death, acute myocardial infarction, stroke) (HR 0.93, CI 0.74-1.15), cardiovascular death (HR 0.84, CI 0.59-1.18), acute myocardial infarction (HR 1.14, CI 0.80-1.63) and stroke (HR 0.72, CI 0.49-1.06). In a sub-study at 18 months, add-on rosiglitazone dual therapy was non-inferior to the combination of sulphonylurea plus metformin for lowering HbA1c. In the final analysis at 5 years, an adjusted mean reduction from baseline in HbA1c of 0.14% for patients on rosiglitazone added to metformin versus an increase of 0.17% for patients taking sulphonylurea added to metformin was seen during treatment with randomised dual-combination therapy ($p<0.0001$ for treatment difference). An adjusted mean reduction in HbA1c of 0.24% was seen for patients taking rosiglitazone added to sulphonylurea, versus a reduction in HbA1c of 0.10% for patients taking metformin added to sulphonylurea, ($p=0.0083$ for treatment difference). There was a significant increase in heart failure (fatal and non-fatal) (HR 2.10, CI 1.35-3.27) and bone fractures (Risk Ratio 1.57, CI 1.26-1.97) in rosiglitazone-containing treatments compared to active control (see sections 4.4 and 4.8). A total of 564 patients withdrew from cardiovascular follow-up, which accounted for 12.3% of rosiglitazone patients and 13% of control patients; representing 7.2% of patient-years lost for cardiovascular events follow-up and 2.0% of patient-years lost for all cause mortality follow-up.

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 three 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).

Medicinal product no longer authorised

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, LDLc and triglyceride levels.

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034
- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021)
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years (p=0.01).

5.2 Pharmacokinetic properties

AVANDAMET

Absorption

No statistically significant difference was observed between the absorption characteristics of rosiglitazone and metformin from the AVANDAMET tablet and those obtained from rosiglitazone maleate and metformin hydrochloride tablets, respectively.

Food had no effect on the AUC of rosiglitazone or metformin when AVANDAMET was administered to healthy volunteers. In the fed state, C_{max} was lower (22% rosiglitazone and 15% metformin) and t_{max} delayed (by approximately 1.5 h rosiglitazone and 0.5 h metformin). This food-effect is not considered clinically significant.

The following statements reflect the pharmacokinetic properties of the individual active substances of AVANDAMET.

Rosiglitazone

Absorption

Absolute bioavailability of rosiglitazone following both a 4 and an 8 mg oral dose is approximately 99%. Rosiglitazone plasma concentrations peak at around 1 h after dosing. Plasma concentrations 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 C_{max} (approximately 20-28%) and a delay in t_{max} (approximately 1.75 h) were observed compared to dosing in the fasting 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.

Distribution

The volume of distribution of rosiglitazone is approximately 14 l in healthy volunteers. Plasma protein binding of rosiglitazone is high (approximately 99.8%) and is not influenced by concentration or age. The protein binding of the major metabolite (a para-hydroxy-sulphate) is very high (> 99.99%).

Metabolism

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 contribution of the major metabolite (a para-hydroxy-sulphate) to

Medicinal product no longer authorised

the overall antihyperglycaemic activity of rosiglitazone has not been fully elucidated in man and it cannot be ruled out that the metabolite may contribute to the activity. However, this raises no safety concern regarding target or special populations as hepatic impairment is contraindicated and the phase III clinical studies included a considerable number of elderly patients and patients with mild to moderate renal impairment.

In vitro studies demonstrate that rosiglitazone is predominantly metabolised by CYP2C8, with a minor contribution by CYP2C9.

Since there is no significant *in vitro* inhibition of CYP1A2, 2A6, 2C19, 2D6, 2E1, 3A or 4A with rosiglitazone, there is a low probability of significant metabolism-based interactions with substances metabolised by these P450 enzymes. Rosiglitazone showed moderate inhibition of CYP2C8 (IC_{50} 18 μM) and low inhibition of CYP2C9 (IC_{50} 50 μM) *in vitro* (see section 4.5). An *in vivo* interaction study with warfarin indicated that rosiglitazone does not interact with CYP2C9 substrates *in vivo*.

Elimination

Total plasma clearance of rosiglitazone is around 3 l/h and the terminal elimination half-life of rosiglitazone is approximately 3-4 h. There is no evidence for unexpected accumulation of rosiglitazone after once or twice daily dosing. The major route of excretion is the urine with approximately two-thirds of the dose being eliminated by this route, whereas faecal elimination accounts for approximately 25% of dose. No intact active substance is excreted in urine or faeces. The terminal half-life for radioactivity was about 130 h indicating that elimination of metabolites is very slow. Accumulation of the metabolites in plasma is expected upon repeated dosing, especially that of the major metabolite (a para-hydroxy-sulphate) for which an 8-fold accumulation is anticipated.

Special populations

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.

Children and adolescents: Population pharmacokinetic analysis including 96 paediatric patients aged 10 to 18 years and weighing 35 to 178 kg suggested similar mean CL/F in children and adults. Individual CL/F in the paediatric population was in the same range as individual adult data. CL/F seemed to be independent of age, but increased with weight in the paediatric population.

Hepatic impairment: In cirrhotic patients with moderate (Child-Pugh B) hepatic impairment, unbound C_{max} and AUC were 2- and 3-fold higher than in normal subjects. The inter-subject variability was large, with a 7-fold difference in unbound AUC between patients.

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.

Metformin

Absorption

After an oral dose of metformin, t_{max} is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 μg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 μg/ml, even at maximum doses.

Medicinal product no longer authorised

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Distribution
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean V_d ranged between 63 – 276 l.

Metabolism
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination
Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3 Preclinical safety data

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
Undesirable effects observed in animal studies with possible relevance to clinical use were as follows: An increase in plasma volume accompanied by decrease in red cell parameters and increase in heart weight. Increases in liver weight, plasma ALT (dog only) and fat tissue were also observed. Similar effects have been seen with other thiazolidinediones.

In reproductive toxicity studies, administration of rosiglitazone to rats during mid-late gestation was associated with foetal death and retarded foetal development. In addition, rosiglitazone inhibited ovarian oestradiol and progesterone synthesis and lowered plasma levels of these hormones resulting in effects on oestrus/menstrual cycles and fertility (see section 4.4).

In an animal model for familial adenomatous polyposis (FAP), treatment with rosiglitazone at 200 times the pharmacologically active dose increased tumour multiplicity in the colon. The relevance of this finding is unknown. However, rosiglitazone promoted differentiation and reversal of mutagenic changes in human colon cancer cells *in vitro*. In addition, rosiglitazone was not genotoxic in a battery of *in vivo* and *in vitro* genotoxicity studies and there was no evidence of colon tumours in lifetime studies of rosiglitazone in two rodent species.

Metformin
Non-clinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Sodium starch glycollate
Hypromellose (E464)
Microcrystalline cellulose (E460)

Medicinal product no longer authorised

Lactose monohydrate
Povidone (E1201)
Magnesium stearate.

Film coat:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol
Iron oxide red (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Opaque blisters (PVC/PVdC/aluminium). Packs of 14, 28, 56, 112 (2x56), 168 (3x56) and 180 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/010-012
EU/1/03/258/014
EU/1/03/258/018
EU/1/03/258/022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 October 2003
Date of latest renewal: 20 October 2008

10. DATE OF REVISION OF THE TEXT

Medicinal product no longer authorised

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.ema.europa.eu

Medicinal product no longer authorised

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

Medicinal product no longer authorised

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Glaxo Wellcome, S.A.
Avenida de Extremadura, 3
09400 Aranda de Duero
Burgos
Spain

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system

The Marketing Authorisation Holder (MAH) must ensure that the system of pharmacovigilance, as described in version 7.2 presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The Marketing Authorisation Holder commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 4 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities.
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached.
1. At the request of the EMEA.

PSURs

Following the renewal of the Marketing Authorisation, the Marketing Authorisation Holder will submit yearly PSURs until otherwise decided by the CHMP.

Medicinal product no longer authorised

ANNEX III

LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (WITH BLUE BOX)
(EXCLUDING MULTIPACKS)

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 1 mg/500 mg film-coated tablets
rosiglitazone/metformin HCl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg of rosiglitazone (as maleate) and 500 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

Contains lactose, see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 tablets
56 tablets
112 tablets
360 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Use only as directed by your doctor.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS

Medicinal product no longer authorised

OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/001 28 tablets
EU/1/03/258/002 56 tablets
EU/1/03/258/003 112 tablets
EU/1/03/258/019 360 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avandamet 1 mg/500 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL (WITH BLUE BOX)
MULTIPACKS ONLY (3x112 TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 1 mg/500 mg film-coated tablets
rosiglitazone/metformin HCl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg of rosiglitazone (as maleate) and 500 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

Contains lactose, see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack comprising 3 packs, each containing 112 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Use only as directed by your doctor.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Medicinal product no longer authorised

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avandamet 1 mg/500 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON (WITHOUT BLUE BOX)
MULTIPACKS ONLY (112 TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 1 mg/500 mg film-coated tablets
rosiglitazone/metformin HCl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg of rosiglitazone (as maleate) and 500 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

Contains lactose, see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

112 tablets.
Component of a multipack comprising 3 packs, each containing 112 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Use only as directed by your doctor.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Medicinal product no longer authorised

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avandamet 1 mg/500 mg

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 1 mg/500 mg tablets
rosiglitazone/metformin HCl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (WITH BLUE BOX)
(EXCLUDING MULTIPACKS)

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 2 mg/500 mg film-coated tablets
rosiglitazone/metformin HCl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg of rosiglitazone (as maleate) and 500 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

Contains lactose, see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 tablets
56 tablets
112 tablets
360 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Use only as directed by your doctor.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS

Medicinal product no longer authorised

OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/004 28 tablets
EU/1/03/258/005 56 tablets
EU/1/03/258/006 112 tablets
EU/1/03/258/020 360 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avandamet 2 mg/500 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL (WITH BLUE BOX)
MULTIPACKS ONLY (3x112 TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 2 mg/500 mg film-coated tablets
rosiglitazone/metformin HCl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg of rosiglitazone (as maleate) and 500 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

Contains lactose, see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack comprising 3 packs, each containing 112 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Use only as directed by your doctor.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Medicinal product no longer authorised

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avandamet 2 mg/500 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON (WITHOUT BLUE BOX)
MULTIPACKS ONLY (3x112 TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 2 mg/500 mg film-coated tablets
rosiglitazone/metformin HCl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg of rosiglitazone (as maleate) and 500 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

Contains lactose, see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

112 tablets.
Component of a multipack comprising 3 packs, each containing 112 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Use only as directed by your doctor.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Medicinal product no longer authorised

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avandamet 2 mg/500 mg

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 2 mg/500 mg tablets
rosiglitazone/metformin HCl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (WITH BLUE BOX)
(EXCLUDING MULTIPACKS)

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 2 mg/1000 mg film-coated tablets
rosiglitazone/metformin HCl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg of rosiglitazone (as maleate) and 1000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

Contains lactose, see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28 tablets
56 tablets
180 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Use only as directed by your doctor.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS

Medicinal product no longer authorised

OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/007 14 tablets
EU/1/03/258/008 28 tablets
EU/1/03/258/009 56 tablets
EU/1/03/258/021 180 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avandamet 2 mg/1000 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL (WITH BLUE BOX)
MULTIPACKS ONLY (2x56 TABLETS, WRAPPED IN CLEAR PLASTIC)
MULTIPACKS ONLY (3x56 TABLETS, PACKED IN BOX)

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 2 mg/1000 mg film-coated tablets
rosiglitazone/metformin HCl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg of rosiglitazone (as maleate) and 1000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

Contains lactose, see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack comprising 2 packs, each containing 56 film-coated tablets.
Multipack comprising 3 packs, each containing 56 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Use only as directed by your doctor.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS

Medicinal product no longer authorised

OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/013, 56 tablets, component of a 112 tablet multipack.
EU/1/03/258/017, 56 tablets, component of a 168 tablet multipack.

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avandamet 2 mg/1000 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON (WITHOUT BLUE BOX)
MULTIPACKS ONLY (56 TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 2 mg/1000 mg film-coated tablets
rosiglitazone/metformin HCl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg of rosiglitazone (as maleate) and 1000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

Contains lactose, see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56 tablets.
Component of a multipack comprising 2 packs, each containing 56 film-coated tablets.

56 tablets.
Component of a multipack comprising 3 packs, each containing 56 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Use only as directed by your doctor.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Medicinal product no longer authorised

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/013, 56 tablets, component of a 112 tablet multipack.
EU/1/03/258/017, 56 tablets, component of a 168 tablet multipack.

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avandamet 2 mg/1000 mg

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 2 mg/1000 mg tablets
rosiglitazone/metformin HCl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (WITH BLUE BOX)
(EXCLUDING MULTIPACKS)

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 4 mg/1000 mg film-coated tablets
rosiglitazone/metformin HCl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 4 mg of rosiglitazone (as maleate) and 1000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

Contains lactose, see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28 tablets
56 tablets
180 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Use only as directed by your doctor.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS

Medicinal product no longer authorised

OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/010 14 tablets
EU/1/03/258/011 28 tablets
EU/1/03/258/012 56 tablets
EU/1/03/258/022 180 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avandamet 4 mg/1000 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL (WITH BLUE BOX)
MULTIPACKS ONLY (2x56 TABLETS, WRAPPED IN CLEAR PLASTIC)
MULTIPACKS ONLY (3x56 TABLETS, PACKED IN BOX)

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 4 mg/1000 mg film-coated tablets
rosiglitazone/metformin HCl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 4 mg of rosiglitazone (as maleate) and 1000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

Contains lactose, see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack comprising 2 packs, each containing 56 film-coated tablets.
Multipack comprising 3 packs, each containing 56 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Use only as directed by your doctor.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS

Medicinal product no longer authorised

OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/014, 56 tablets, component of a 112 tablet multipack.
EU/1/03/258/018, 56 tablets, component of a 168 tablet multipack.

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avandamet 4 mg/1000 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON (WITHOUT BLUE BOX)
MULTIPACKS ONLY (56 TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 4 mg/1000 mg film-coated tablets
rosiglitazone/metformin HCl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 4 mg of rosiglitazone (as maleate) and 1000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

Contains lactose, see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56 tablets.
Component of a multipack comprising 2 packs, each containing 56 film-coated tablets.

56 tablets.
Component of a multipack comprising 3 packs, each containing 56 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Use only as directed by your doctor.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Medicinal product no longer authorised

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/258/014, 56 tablets, component of a 112 tablet multipack.
EU/1/03/258/018, 56 tablets, component of a 168 tablet multipack.

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avandamet 4 mg/1000 mg

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

AVANDAMET 4 mg/1000 mg tablets
rosiglitazone/metformin HCl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Medicinal product no longer authorised

PACKAGE LEAFLET: INFORMATION FOR THE USER

AVANDAMET 1 mg/500 mg film-coated tablets
AVANDAMET 2 mg/500 mg film-coated tablets
AVANDAMET 2 mg/1000 mg film-coated tablets
AVANDAMET 4 mg/1000 mg film-coated tablets
rosiglitazone/metformin HCl

Read all of this leaflet carefully before you start taking this medicine.
- **Keep this leaflet. You may need to read it again.**
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- **If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.**

In this leaflet:

1. WHAT AVANDAMET IS AND WHAT IT IS USED FOR

Avandamet tablets are a combination of two different medicines called *rosiglitazone* and *metformin.* These two medicines are used to treat **type 2 diabetes.**

People with type 2 diabetes either don't make enough insulin (a hormone that controls blood sugar levels), or don't respond normally to the insulin their body makes. Rosiglitazone and metformin work together so your body makes better use of the insulin it produces, and this helps reduce your blood sugar to a normal level. Avandamet can be used alone or with a sulphonylurea, another medicine for diabetes.

2. BEFORE YOU TAKE AVANDAMET

To help manage your diabetes, it is important that you follow any diet and lifestyle advice from your doctor as well as taking Avandamet.

Don't take Avandamet:
- **if you are allergic** (*hypersensitive*) to rosiglitazone or metformin or any of the other ingredients of Avandamet (*listed in Section 6)*
- **if you have had a heart attack or severe angina,** that's being treated in hospital
- **if you have heart failure,** or have had heart failure in the past
- **if you have severe breathing difficulties**
- **if you have liver disease**
- **if you are a heavy drinker of alcohol** – if you regularly drink a lot, or if you have occasional sessions of heavy drinking (binge drinking)
- **if you have had diabetic ketoacidosis** (a complication of diabetes causing rapid weight loss, nausea or vomiting)
- **if you have kidney disease**

Medicinal product no longer authorised

- **if you are very dehydrated or have a severe infection** *(see 'While you take Avandamet your doctor needs to know' later in Section 2*)
- **if you are going to have an X-ray using an injected dye** *(see 'While you take Avandamet your doctor needs to know' later in Section 2*)
- **if you are breast-feeding** *(see 'Pregnancy and breast-feeding' later in Section 2*).

➔ **Check with your doctor** if you think any of these apply to you. **Don't take Avandamet.**

Take special care with Avandamet

Avandamet is not recommended for people aged under 18, as the safety and effectiveness are not known.

If you have been diagnosed with angina (chest pain), or peripheral arterial disease (reduced blood flow to the legs):

➔ **Check with your doctor,** as Avandamet may not be suitable for you.

Conditions to look out for
Avandamet and other medicines for diabetes can make some existing conditions worse, or cause serious side effects. You must look out for certain symptoms while you are taking Avandamet, to reduce the risk of any problems. See '*Conditions you need to look out for'* **in Section 4.**

Ovulation may restart
Women who are infertile due to a condition affecting their ovaries (such as *Polycystic Ovarian Syndrome*), may start ovulating again when they start taking Avandamet. If this applies to you, use appropriate contraception to avoid the possibility of an unplanned pregnancy *(see 'Pregnancy and breast-feeding' later in Section 2).*

Your kidney function will be checked
Your kidneys should be checked at least once a year – more often if you are over 65, or if your kidney function is close to abnormal.

While you take Avandamet your doctor needs to know:

- **if you become dehydrated –** for example, after severe vomiting, diarrhoea or fever. These can lead to severe loss of water (*dehydration*). Speak to your doctor, as you may need to stop taking Avandamet for a short while**.**
- **if you are going to have an operation under general anaesthetic.** Your doctor will advise you to stop taking Avandamet for at least 48 hours before and after the operation.
- **if you are going to have an X-ray using an injected dye.** Your doctor will advise you to stop taking Avandamet before the X-ray and for 48 hours after it. The doctor will check your kidney function before restarting treatment.

Medicinal product no longer authorised

Taking other medicines
Tell your doctor or pharmacist if you are taking any other medicines, if you've taken any recently, or if you start taking new ones. This includes herbal medicines and other medicines you bought without a prescription.

Certain medicines are especially likely to affect the amount of sugar in your blood:
- steroids (used to treat **inflammation**) such as prednisolone or dexamethasone
- beta-2-agonists (used to treat **asthma**), such as salbutamol or salmeterol
- diuretics (used to **get rid of water**), such as furosemide or indapamide
- ACE inhibitors (used to treat **high blood pressure**), such as enalapril or captopril
- gemfibrozil (used to **lower cholesterol**)
- rifampicin (used to treat **tuberculosis** and other infections)
- cimetidine (used to reduce **stomach acid**).

➔ **Tell a doctor or pharmacist if you are taking any of these.** Your blood sugar will be checked, and your dose of Avandamet may need to be changed.

Pregnancy and breast-feeding
- **Avandamet is not recommended during pregnancy.** If you are pregnant or could be pregnant, tell your doctor before you take Avandamet.

- **Don't breast-feed** while you are taking Avandamet. The ingredients may pass into breast milk and so may harm your baby.

Driving and using machines
This medicine should not affect your ability to drive or use machines.

Avandamet contains lactose
Avandamet tablets contain a small amount of lactose. Patients who are intolerant to lactose or have a rare hereditary problem of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption **should not take this medicine.**

3. HOW TO TAKE AVANDAMET

Always take Avandamet tablets exactly as your doctor has told you. Do not take more than the recommended dose. Check with your doctor or pharmacist if you are not sure.

How much to take
The usual starting dose is one combined tablet (2 mg rosiglitazone and 1000 mg metformin), taken twice a day, morning and evening. (You can also take this dose as two 1 mg/500 mg tablets, twice a day.)

After about 8 weeks your doctor may need to increase your dose. The maximum dose is 4 mg rosiglitazone and 1000 mg metformin, taken twice a day. (You can also take this dose as two 2 mg/500 mg tablets, twice a day.)

How to take
Swallow the tablets with some water.

It is best to take Avandamet with food, or just after food. This helps to reduce any problems with your stomach (including indigestion, nausea, vomiting and diarrhoea).

Take your tablets around the same time every day and follow any dietary advice that your doctor has given you.

If you take more Avandamet than you should

Medicinal product no longer authorised

If you accidentally take too many tablets, contact your doctor or pharmacist for advice.

If you forget to take Avandamet
Don't take extra tablets to make up for a missed dose. Just take your next dose at the usual time.

Don't stop taking Avandamet
Take Avandamet for as long as your doctor recommends. If you stop taking Avandamet, your blood sugar will not be controlled, and you may become unwell. Talk to your doctor if you want to stop.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Avandamet can cause side effects, but not everybody gets them.

Conditions you need to look out for

Allergic reactions: These are very rare in people taking Avandamet. Signs include:
- raised and itchy rash (*hives*)
- swelling, sometimes of the face or mouth (*angioedema*), causing difficulty in breathing
- collapse.

➔ **Contact a doctor immediately** if you get any of these symptoms. **Stop taking Avandamet.**

Lactic acidosis: An increase in the amount of lactic acid in the blood *(lactic acidosis)* is a very rare side effect of metformin. This most often affects people who have severe kidney disease. Symptoms of lactic acidosis include:
- rapid breathing
- feeling cold
- stomach pain, nausea and vomiting.

➔ **Contact a doctor immediately** if you get these symptoms. **Stop taking Avandamet.**

Fluid retention and heart failure: Avandamet can cause you to retain water (*fluid retention*) which leads to swelling and weight gain. Extra body fluid can make some existing heart problems worse or lead to heart failure. This is more likely if you are also taking other medicines for your diabetes (like insulin), if you have kidney problems, or if you are over 65. **Check your weight regularly; if it goes up rapidly, tell your doctor.** Symptoms of heart failure include:
- shortness of breath, waking up short of breath at night
- getting tired easily after light physical activity such as walking
- rapid increase in your weight
- swollen ankles or feet.

➔ **Tell your doctor as soon as possible** if you get any of these symptoms - either for the first time or if they get worse.

Low blood sugar (*hypoglycaemia*): If you are taking Avandamet with other medicines for diabetes, it is more likely that your blood sugar could fall below the normal level. Early symptoms of low blood sugar are:
- shaking, sweating, faintness
- nervousness, palpitations
- hunger.

The severity can increase, leading to confusion and loss of consciousness.

➔ **Tell your doctor as soon as possible** if you get any of these symptoms. The dose of your medicines may need to be reduced.

Liver problems: Before you start taking Avandamet you will have a blood sample taken to check your liver function. This check may be repeated at intervals. These may be signs of liver problems:
- nausea and vomiting
- stomach (*abdominal*) pain

Medicinal product no longer authorised

- loss of appetite
- dark-coloured urine.

➔ **Tell your doctor as soon as possible** if you get these symptoms.

Eye problems: Swelling of the retina at the back of the eye which can cause blurred vision (*macular oedema*) can be a problem for people with diabetes. New or worse cases of macular oedema have occurred on rare occasions in people taking Avandamet and similar medicines.

➔ **Discuss with your doctor** any concerns about your eyesight.

Broken bones: Bone fractures can occur in people with diabetes. The chances of this happening may be higher in people, particularly women, taking rosiglitazone for more than one year. The most common are breaks in feet, hands and arms.

Very common side effects
These may affect **more than 1 in 10** people:
- stomach pain, feeling sick (*nausea*), vomiting, diarrhoea or loss of appetite.

Common side effects
These may affect **up to 1 in 10** people:
- chest pain (*angina*)
- broken bones
- reduction in blood count (*anaemia*)
- small increases in blood cholesterol, increased amount of fats in the blood
- increased weight, increased appetite
- dizziness
- constipation
- lower blood sugar than normal (*hypoglycaemia*)
- swelling (*oedema)* due to water retention
- metallic taste in the mouth.

Rare side effects
These may affect **up to 1 in 1,000** people:
- fluid in the lungs (*pulmonary oedema*) causing breathlessness
- heart failure
- swelling of the retina at the back of the eye (*macular oedema*)
- liver doesn't function as well as it should (*increase in liver enzymes*).

Very rare side effects
These may affect **up to 1 in 10,000** people:
- allergic reactions
- inflammation of the liver (*hepatitis*)
- decrease in amount of vitamin B_{12} in the blood
- rapid and excessive weight gain caused by fluid retention
- increase of lactic acid in the blood.

If you get side effects

➔ **Tell your doctor or pharmacist** if any of the side effects listed gets severe or troublesome, or if you notice any side effects not listed in this leaflet.

5. HOW TO STORE AVANDAMET

Keep out of the reach and sight of children.

Do not use Avandamet after the expiry date shown on the pack.

Medicinal product no longer authorised

This medicine does not require any special storage conditions.

If you have any unwanted tablets, don't put them in waste water or household rubbish. Ask your pharmacist how to dispose of tablets you don't need. This will help to protect the environment.

6. FURTHER INFORMATION

What Avandamet contains
The active substances are rosiglitazone and metformin. Avandamet tablets come in different strengths. Each tablet contains either: 1 mg rosiglitazone and 500 mg metformin; 2 mg rosiglitazone and 500 mg metformin; 2 mg rosiglitazone and 1000 mg metformin or 4 mg rosiglitazone and 1000 mg metformin.

The other ingredients are: sodium starch glycollate, hypromellose (E464), microcrystalline cellulose (E460), lactose monohydrate, povidone (E1201), magnesium stearate, titanium dioxide (E171), macrogol, iron oxide yellow or red (E172).

What Avandamet looks like and contents of the pack
Avandamet 1 mg/500 mg tablets are yellow and marked "gsk" on one side and "1/500" on the other.
Avandamet 2 mg/500 mg tablets are pale pink, marked "gsk" on one side and "2/500" on the other.
These strengths are supplied in blister packs containing 28, 56, 112, 3x112 or 360 film-coated tablets.

Avandamet 2 mg/1000 mg tablets are yellow, marked "gsk" on one side and "2/1000" on the other.
Avandamet 4 mg/1000 mg tablets are pink, marked "gsk" on one side and "4/1000" on the other.
These strengths are supplied in blister packs containing 14, 28, 56, 2x56, 3x56 or 180 film-coated tablets.

Not all pack sizes or tablet strengths may be available in your country.

Marketing Authorisation Holder: SmithKline Beecham Ltd, 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom.

Manufacturer: Glaxo Wellcome S.A., Avenida de Extremadura 3, 09400 Aranda de Duero, Burgos, Spain.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

Medicinal product no longer authorised

België/Belgique/Belgien
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 (0)2 656 21 11

България
ГлаксоСмитКлайн ЕООД
Тел.: + 359 2 953 10 34

Česká republika
GlaxoSmithKline s.r.o.
Tel: + 420 222 001 111
gsk.czmail@gsk.com

Danmark
GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
dk-info@gsk.com

Deutschland
GlaxoSmithKline GmbH & Co. KG
Tel.: + 49 (0)89 36044 8701
produkt.info@gsk.com

Eesti
GlaxoSmithKline Eesti OÜ
Tel: + 372 6676 900
estonia@gsk.com

Ελλάδα
GlaxoSmithKline A.E.B.E.
Τηλ: + 30 210 68 82 100

España
GlaxoSmithKline, S.A.
Tel: + 34 902 202 700
es-ci@gsk.com

France
Laboratoire GlaxoSmithKline
Tél.: + 33 (0)1 39 17 84 44
diam@gsk.com

Ireland
GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Ísland
GlaxoSmithKline ehf.
Sími: + 354 530 3700

Luxembourg/Luxemburg
GlaxoSmithKline s.a./n.v.
Belgique/Belgien
Tél/Tel: + 32 (0)2 656 21 11

Magyarország
GlaxoSmithKline Kft.
Tel.: + 36 1 225 5300

Malta
GlaxoSmithKline Malta
Tel: + 356 21 238131

Nederland
GlaxoSmithKline BV
Tel: + 31 (0)30 6938100
nlinfo@gsk.com

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00
firmapost@gsk.no

Österreich
GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

Polska
GSK Commercial Sp. z o.o.
Tel.: + 48 (0)22 576 9000

Portugal
GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România
GlaxoSmithKline (GSK) S.R.L.
Tel: + 4021 3028 208

Slovenija
GlaxoSmithKline d.o.o.
Tel: + 386 (0)1 280 25 00
medical.x.si@gsk.com

Slovenská republika
GlaxoSmithKline Slovakia s. r. o.
Tel: + 421 (0)2 48 26 11 11
recepcia.sk@gsk.com

Medicinal product no longer authorised

Italia
GlaxoSmithKline S.p.A.
Tel: + 39 (0)45 9218 111

Κύπρος
GlaxoSmithKline Cyprus Ltd
Τηλ: + 357 22 39 70 00

Latvija
GlaxoSmithKline Latvia SIA
Tel: + 371 67312687
lv-epasts@gsk.com

Lietuva
GlaxoSmithKline Lietuva UAB
Tel: + 370 5 264 90 00
info.lt@gsk.com

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30
Finland.tuoteinfo@gsk.com

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

United Kingdom
GlaxoSmithKline UK
Tel: + 44 (0)800 221441
customercontactuk@gsk.com

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.ema.europa.eu

Medicinal product no longer authorised