1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 4 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains rosiglitazone maleate corresponding to 4 mg rosiglitazone.

Excipient
Contains lactose (approximately 105 mg).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Orange film-coated tablets debossed with “GSK” on one side and "4" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rosiglitazone is indicated in the treatment of type 2 diabetes mellitus:

as **monotherapy**
– in patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance

as **dual oral therapy** in combination with
– metformin, in patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin
– a sulphonylurea, only in patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite monotherapy with a sulphonylurea

as **triple oral therapy** in combination with
– metformin and a sulphonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy (see section 4.4).

4.2 Posology and method of administration

Rosiglitazone therapy is usually initiated at 4 mg/day. This dose can be increased to 8 mg/day after eight weeks if greater glycaemic control is required. In patients administered rosiglitazone in combination with a sulphonylurea, an increase in rosiglitazone 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 4.4 and 4.8).

Rosiglitazone may be given once or twice a day.

Rosiglitazone may be taken with or without food.

Elderly (see section 4.4 Fluid retention and cardiac failure)
No dose adjustment is required in the elderly.

Patients with renal impairment (see section 4.4 Fluid retention and cardiac failure)
No dose adjustment is required in patients with mild and moderate renal insufficiency. Limited data are available in patients with severe renal insufficiency (creatinine clearance < 30 ml/min) and therefore rosiglitazone should be used with caution in these patients.

Patients with hepatic impairment
Rosiglitazone should not be used in patients with hepatic impairment.

Children and adolescents
There are no data available on the use of rosiglitazone in patients under 10 years of age. For children aged 10 to 17 years, there are limited data on rosiglitazone as monotherapy (see sections 5.1 and 5.2). The available data do not support efficacy in the paediatric population and therefore such use is not recommended.

4.3 Contraindications

Use of rosiglitazone is contraindicated in patients with:

- known hypersensitivity to rosiglitazone or to any of the excipients
- cardiac failure or history of cardiac failure (NYHA class I to IV)
- an Acute Coronary Syndrome (unstable angina, NSTEMI and STEMI) (see section 4.4)
- hepatic impairment
- diabetic ketoacidosis or diabetic pre-coma.

4.4 Special warnings and precautions for use

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 or 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. Increased monitoring of the patient is recommended if rosiglitazone is used in combination with metformin and insulin. Rosiglitazone should be discontinued if any deterioration in cardiac status occurs.

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 and rosiglitazone are 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.

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 (see section 4.8). There is limited experience with rosiglitazone in patients with elevated liver enzymes (ALT >2.5X upper limit of normal). Therefore, liver enzymes should be checked prior to the initiation of therapy with rosiglitazone in all patients and periodically thereafter based on clinical judgement. Therapy with rosiglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal) or with any other evidence of liver disease. If ALT levels are increased to >3X upper limit of normal during rosiglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain >3X 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 rosiglitazone should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug 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 rosiglitazone.

Hypoglycaemia
Patients receiving rosiglitazone in combination therapy with a sulphonylurea or with 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.

Triple oral therapy
The use of rosiglitazone in triple oral therapy, in combination with metformin and a sulphonylurea, may be associated with increased risks for fluid retention and heart failure, as well as hypoglycaemia (see section 4.8). Increased monitoring of the patient is recommended and adjustment of the dose of sulphonylurea may be necessary. The decision to initiate triple oral therapy should include consideration of the alternative to switch the patient to insulin.

Bone disorders
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.

Others
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 and if a patient wishes to become pregnant or if pregnancy occurs the treatment should be discontinued (see section 4.6).

Rosiglitazone should be used with caution in patients with severe renal insufficiency (creatinine clearance < 30 ml/min).

Rosiglitazone should be used with caution during concomitant administration of CYP2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin). Glycaemic control should be monitored closely. Rosiglitazone dose adjustment within the recommended posology or changes in diabetic treatment should be considered (see section 4.5).

AVANDIA 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

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, 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 with the oral anti-diabetic agents metformin, glibenclamide and acarbose did not result in any clinically relevant pharmacokinetic interactions with rosiglitazone. Moderate ingestion of alcohol with rosiglitazone has no effect on glycaemic control.

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

4.6 Pregnancy and lactation

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. Rosiglitazone should not be used during pregnancy.

Rosiglitazone has been detected in the milk of experimental animals. It is not known whether breast-feeding will lead to exposure of the infant to drug. Rosiglitazone should therefore not be used in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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. 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, < 1/10; and uncommon ≥ 1/1000, < 1/100.

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.

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

Adverse reaction	**Frequency of adverse reaction by treatment regimen**			
	RSG	**RSG + MET**	**RSG + SU**	**RSG +MET +SU**
Blood and the lymphatic system disorders				
anaemia	Common	Common	Common	Common
leucopaenia			Common	
thrombocytopaenia			Common	
granulocytopaenia				Common
Metabolism and nutrition disorders				
hypercholesterolaemia[1]	Common	Common	Common	Common
hypertriglyceridaemia	Common		Common	
hyperlipaemia	Common	Common	Common	Common
weight increase	Common	Common	Common	Common
increased appetite	Common		Uncommon	
hypoglycaemia		Common	Very common	Very common
Nervous system disorders				
dizziness*		Common	Common	
headache*				Common
Cardiac disorders				
cardiac failure[2]		Common	Common	Common
cardiac ischaemia[3*]	Common	Common	Common	Common

Gastrointestinal disorders				
constipation	Common	Common	Common	Common
Musculoskeletal and connective tissue disorders				
bone fractures[4]	Common	Common	Common	
myalgia*				Common
General disorders and administration site conditions				
oedema	Common	Common	Very common	Very common

RSG - Rosiglitazone monotherapy; RSG + MET - Rosiglitazone with metformin; RSG + SU Rosiglitazone with sulphonylurea; RSG + MET + SU - Rosiglitazone with metformin and sulphonylurea

*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 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%. Moreover in patients with congestive heart failure NYHA class I-II, a placebo-controlled one-year trial demonstrated worsening or possible worsening of heart failure 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. Frequencies are defined as: rare ≥1/10,000, <1/1000 and very rare <1/10,000 including isolated reports.

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

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, pruritus, 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.

4.9 Overdose

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

In the event of an overdose, it is recommended that appropriate supportive treatment should be initiated, as dictated by the patient's clinical status. Rosiglitazone is highly protein bound and is not cleared by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: oral blood glucose lowering drugs, thiazolidinediones, ATC code: A10 BG 02

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

Preclinical data
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 (para-hydroxy-sulphate) with high affinity to the soluble human PPARγ, exhibited relatively high potency in a glucose tolerance assay in obese mouse. The clinical relevance of this observation has not been fully elucidated.

Clinical trials data
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 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, dual oral therapy of rosiglitazone with a sulphonylurea or 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 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 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

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.

5.2 Pharmacokinetic properties

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 hour 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% to 28%) and a delay in t_{max} (ca.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 litres 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 (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 (para-hydroxy-sulphate) to the overall anti-diabetic 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 to 4 hours. 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 drug is excreted in urine or faeces. The terminal half-life for radioactivity was about 130 hours 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 (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.

5.3 Preclinical safety data

Adverse 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Sodium starch glycollate (Type A)
hypromellose
microcrystalline cellulose
lactose monohydrate
magnesium stearate.

Film coating (Opadry orange OY-L-23028)**:**
Hypromellose 6cP
Titanium dioxide E171
Macrogol 3000
Purified talc
Lactose monohydrate
Glycerol triacetate
Iron oxide red E172
Iron oxide yellow E172.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 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 blister packs (PVC/ aluminium). 7, 28, 56, 84, 90 or 112 film-coated tablets or 56 film-coated tablets, unit dose pack.

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/1/00/137/005-009, EU/1/00/137/014, EU/1/00/137/017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 July 2000
Date of latest renewal: 11 July 2005

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