ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AVAGLIM 4 mg/4 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains rosiglitazone maleate corresponding to 4 mg rosiglitazone and 4 mg glimepiride.

Excipient
- contains lactose (approximately 104 mg)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, rounded triangular tablet with "gsk" debossed on one side and "4/4" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AVAGLIM is indicated in the treatment of type 2 diabetes mellitus patients who are unable to achieve sufficient glycaemic control on optimal dosage of sulphonylurea monotherapy, and for whom metformin is inappropriate because of contraindication or intolerance.

4.2 Posology and method of administration

AVAGLIM therapy should be individualised for each patient. Before therapy is initiated with AVAGLIM appropriate clinical evaluation should be made to assess the patient's risk of developing hypoglycaemia (see section 4.4).

AVAGLIM should be taken once daily shortly before or during a meal (usually the first main meal of the day). If a dose is forgotten, the following dose must not be increased.

For patients inadequately controlled on glimepiride monotherapy (typically 4 mg). Concomitant administration should be considered before the patient is switched to AVAGLIM. Where clinically appropriate, direct change from glimepiride monotherapy to AVAGLIM may be considered**.** The starting dose is 4 mg/day rosiglitazone plus 4 mg/day glimepiride (given as one tablet AVAGLIM 4 mg/4 mg).

Patients unable to achieve glycaemic control on at least half-maximum dose of other sulphonylurea monotherapy (except chlorpropamide, see section 4.4). Rosiglitazone 4 mg should be administered concomitantly with the dose of sulphonylurea already being taken. Once glycaemic control is stable at these doses, AVAGLIM may be introduced at a starting dose of 4 mg rosiglitazone/4 mg glimepiride once daily.

AVAGLIM may be used to substitute concomitant sulphonylurea and rosiglitazone in established dual oral therapy providing the patient has achieved at least half-maximum dose of sulphonylurea.

The dose of the rosiglitazone component can be increased after 8 weeks if required. The maximum recommended daily dose is 8 mg rosiglitazone/4 mg glimepiride (given as one AVAGLIM tablet 8 mg/4 mg, once daily). 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 4.4 and 4.8).

If hypoglycaemic symptoms occur, the patient should revert to concomitant therapy and adjust the glimepiride dose as appropriate.

Elderly
Due to the potential for decreased renal function the initiation and maintenance of therapy with AVAGLIM in elderly patients should be under close medical supervision due to an increased susceptibility to hypoglycaemia (see section 4.4).

Patients with renal impairment
Mild or moderate renal impairment (creatinine clearance 30 to 80 ml/min):
- Patients changing to AVAGLIM from sulphonylurea therapies other than glimepiride may be at an increased risk of hypoglycaemia (see section 4.4). Appropriate monitoring is advised.

AVAGLIM is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 ml/min, see section 4.3).

Patients with hepatic impairment
AVAGLIM is contraindicated in patients with hepatic impairment (see section 4.3).

Children and adolescents
AVAGLIM is not recommended for use in children below 18 years of age as there are no data available on its safety and efficacy.

4.3 Contraindications

Use of AVAGLIM is contraindicated in patients with:

- hypersensitivity to rosiglitazone, glimepiride, other sulphonylureas or sulphonamides 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
- severe renal impairment i.e. creatinine clearance less than 30 ml/min (including renal dialysis).
- insulin dependant diabetes
- diabetic ketoacidosis or diabetic coma.

4.4 Special warnings and precautions for use

AVAGLIM is not indicated for combination use with metformin and therefore should not be used in triple oral therapy of diabetes.

The following statements refer to AVAGLIM or the two individual active substances (rosiglitazone and glimepiride).

Hypoglycaemia
Patients receiving AVAGLIM may be at risk of dose-related hypoglycaemia (see section 4.8). It is advised that patients established on rosiglitazone and chlorpropamide concomitant therapy should not switch to AVAGLIM as chlorpropamide has a long half-life which may increase the risk of hypoglycaemia. If risk factors for hypoglycaemia are present (including renal insufficiency, low body weight, malnourishment, co-administration with certain other medicinal products (see section 4.5) or if the patient's life-style changes) it may be necessary to revert to concomitant therapy and down titrate the glimepiride dose. A switch to insulin should be considered in stress situations (e.g. trauma, surgery, infections).

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 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. 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 with rosiglitazone (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 AVAGLIM in all patients and periodically thereafter based on clinical judgement. Therapy with AVAGLIM 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 AVAGLIM 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.

Patients with renal impairment
Patients with mild or moderate renal impairment (creatinine clearance 30 to 80 ml/min) may be at an increased risk of hypoglycaemia (see sections 4.2, 4.3 and 4.4). Appropriate monitoring is advised.

Premenopausal anovulatory women
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).

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.

Haematological monitoring
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 AVAGLIM.

Periodic haematological monitoring (especially leucocytes and thrombocytes) are required during treatment with AVAGLIM.

Treatment of patients with G6PD-deficiency with sulphonylurea agents can lead to haemolytic anaemia. Since glimepiride belongs to the chemical class of sulphonylurea drugs, caution should be used in patients with G6PD-deficiency and a non-sulphonylurea alternative should be considered.

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.

Administration with other medicinal products
Rosiglitazone should be used with caution during concomitant administration of CYP2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin). Glimepiride should be used with caution during concomitant administration of CYP2C9 inhibitors (e.g. fluconazole) or inducers (see section 4.5). Glycaemic control should be monitored closely. AVAGLIM dose adjustment within the recommended posology or changes in diabetic treatment should be considered.

Lactose intolerance
AVAGLIM 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 AVAGLIM. 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 glimepiride).

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

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

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).

Concomitant administration of rosiglitazone with the oral anti-diabetic agents metformin, glimepiride, 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.

Glimepiride
If glimepiride is taken simultaneously with certain other medicines, both undesired increases and decreases in the hypoglycaemic action of glimepiride can occur. For this reason, other medicines should only be taken with the knowledge (or at the prescription) of the doctor.

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole

Results from an vivo interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.

Based on the experience with glimepiride and with other sulphonylureas the following interactions have to be mentioned.

Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following drugs is taken, for example:

phenylbutazone, azapropazon and oxyfenbutazone,
insulin and oral antidiabetic products,
metformin,
salicylates and p-amino-salicylic acid,
anabolic steroids and male sex hormones,
chloramphenicol,
coumarin anticoagulants,
fenfluramine,
fibrates,
ACE inhibitors,
fluoxetine,
allopurinol,
sympatholytics,
cyclo-, tro-and iphosphamides,
sulphinpyrazone,
certain long acting sulphonamides,
tetracyclines,
MAO-inhibitors,
quinolone antibiotics,
probenecid,
miconazol,
pentoxifylline (high dose parenteral),
tritoqualine,
fluconazole.

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following drugs is taken, for example:

oestrogens and progestagens,
saluretics, thiazide diuretics,
thyroid stimulating agents, glucocorticoids,
phenothiazine derivatives, chlorpromazine,
adrenaline and sympathicomimetics,
nicotinic acid (high dosages) and nicotinic acid derivatives,
laxatives (long term use),
phenytoin, diazoxide,
glucagon, barbiturates and rifampicin,
acetozolamide.

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

Under the influence of sympatholytic drugs such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counterregulation to hypoglycaemia may be reduced or absent.

Alcohol intake may potentiate or weaken the hypoglycaemic action of glimepiride in an unpredictable fashion.

Glimepiride may either potentiate or weaken the effects of coumarin derivatives.

4.6 Pregnancy and lactation

For AVAGLIM 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 either active substance (rosiglitazone and glimepiride) in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Therefore, AVAGLIM should not be used during pregnancy and the use of insulin is recommended. If a patient wishes to become pregnant or if pregnancy occurs, treatment with AVAGLIM should be discontinued.

Both rosiglitazone and glimepiride have been detected in the milk of experimental animals. It is not known whether breast-feeding will lead to exposure of the infant to medicinal product. Therefore, AVAGLIM should not be used during lactation.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. Nevertheless, the potential for hypoglycaemia should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills (e.g. driving).

4.8 Undesirable effects

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

AVAGLIM
Data from double-blind studies confirm that the safety profile of concomitant rosiglitazone and glimepiride is similar to that of the combined adverse reaction profile for the two active substances. Limited data with AVAGLIM is also consistent with this combined adverse reaction profile.

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. 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 with rosiglitazone

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

*The frequency category for the background incidence of this event, 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 or dual 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 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 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.

Glimepiride

Clinical trial data and post-marketing data
Table 3 presents adverse reactions by system organ class and by frequency category based on experience with glimepiride and other sulphonylureas. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥1/10,000, <1/1000) and very rare (<1/10,000 including isolated reports).

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

Adverse reaction	Frequency
Blood and lymphatic system disorders	
agranulocytosis	Rare
granulocytopenia	Rare
pancytopenia	Rare
haemolytic anaemia	Rare
thrombocytopenia	Rare
leukopenia	Rare
erythrocytopenia	Rare
Immune system disorders[6]	
allergic vasculitis	Very rare
hypersensitivity reactions[7]	Very rare
Metabolism and nutrition disorders	
hypoglycaemia[8]	Very common

Gastrointestinal disorders	
vomiting	Very rare
diarrhoea	Very rare
nausea	Very rare
abdominal distension	Very rare
abdominal pain	Very rare
abdominal discomfort	Very rare
Hepatobiliary disorders[9]	
hepatitis[10]	Very rare
impairment of liver function (e.g. with cholestasis and jaundice)	Very rare
Skin and subcutaneous tissue disorders[11]	
hypersensitivity of the skin to light	Very rare
Investigations	
serum sodium decrease	Very rare

[6] Cross-allergenicity with sulphonylureas, sulphonamides or related substances is possible.
[7] Mild hypersensitivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock.

[8] Based on what is known of other sulphonylureas, hypoglycaemia may be prolonged. Rarely hypoglycaemic reactions can occur immediately and may be severe and not always easy to correct.

[9] Elevation of liver enzymes may occur.
[10] Hepatitis may progress to liver failure.

[11] Hypersensitivity reactions of the skin may occur as itching, rash and urticaria.

Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.

4.9 Overdose

No data are available with regard to overdose of AVAGLIM.

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.

Overdose of sulphonylureas, including glimepiride, can result in severe life-threatening hypoglycaemia lasting 12 to 72 hours, which may recur after apparent recovery. The symptoms may be delayed for up to 24 hours after ingestion. Hospitalisation should be considered as appropriate.

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 and glimepiride are both highly protein bound and would not be expected to be cleared by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of oral blood glucose lowering drugs, ATC code: A10BD04.

AVAGLIM combines two antidiabetic 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 glimepiride, a member of the sulphonylurea class. Thiazolidinediones act primarily by reducing insulin resistance and sulphonylureas act primarily by stimulating release of insulin from functioning pancreatic β-cells. A study comparing AVAGLIM to monotherapy rosiglitazone or glimepiride demonstrated incremental benefit in control of glycaemia of the fixed-dose combination over monotherapy. No new safety findings were observed. The clinical trial program in support of this fixed dose combination only compared rosiglitazone and glimepiride to glimepiride monotherapy and not to monotherapy with other sulphonylureas.

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 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.

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.

Glimepiride
Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group. It may be used in non-insulin dependent diabetes mellitus.
Glimepiride acts mainly by stimulating the release of insulin from the beta cells of the pancreas. As with other sulphonylureas, this effect is based on an improvement in responsiveness of pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects, also postulated for other sulphonylureas.

Sulphonylureas regulate insulin secretion by closing the ATP-dependent potassium channels in the beta cell membrane. Closure of the potassium channels leads to depolarisation of the beta cell and results by opening of the calcium channels – to an increased influx of calcium into the cell. This leads to a release of insulin by exocytosis.

Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel but which differs from the usual sulphonylurea binding site.

Extrapancreatic effects include an improvement in insulin sensitivity of peripheral tissue and a reduction in hepatic uptake of insulin.
Glimepiride very rapidly increases the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulation of glucose uptake.
Glimepiride increases the activity of glycosyl-phosphatidylinositol-specific phospholipase C, which may be associated with drug-induced lipogenesis and glycogenesis in isolated fat and muscle cells.
Glimepiride inhibits the hepatic glucose production by increasing the intracellular concentration of fructose-2,6 bisphosphate, which in turn inhibits gluconeogenesis.

The minimum effective oral dose is approximately 0.6 mg. The effect of glimepiride is dose-dependent and reproducible. The physiological response to acute physical exercise, a reduction in insulin secretion, is maintained during treatment with glimepiride.
There was no significant difference in the effect regardless of whether the drug was taken 30 minutes before or immediately before a meal. In diabetic patients, good metabolic control over 24 hours can be achieved with a single daily dose.
Although the hydroxy metabolite of glimepiride caused a small but significant reduction in serum glucose, it accounts for only a minor part of the total drug effect.

5.2 Pharmacokinetic properties

AVAGLIM

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

In a bioequivalence study under fasted conditions, the AUC and C_{max} of rosiglitazone and the AUC of glimepiride following a single dose of a 4 mg/4 mg combination tablet were bioequivalent to concomitant administration of rosiglitazone 4 mg and glimepiride 4 mg.

In the fed state, the rate and extent of absorption of the rosiglitazone-glimepiride 4 mg/4 mg combination were equivalent to concomitant administration of 4 mg rosiglitazone and 4 mg glimepiride. Administration of the 4 mg/4 mg combination with food led to an increase in glimepiride exposure compared to that observed on administration in the fasted state. Glimepiride AUC_{0-t}, AUC_{0-inf} and C_{max} were increased by 30%, 19% and 55% respectively, on average. For rosiglitazone, C_{max} values were decreased by approximately 32% with food.

The AUC and C_{max} of glimepiride increased in a dose-proportional manner following administration of rosiglitazone-glimepiride 4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg.

The following statements reflect the pharmacokinetic properties of the individual components of AVAGLIM.

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 fasted state. These small changes are not clinically significant and, therefore, it is not necessary to administer rosiglitazone at any particular time in relation to meals. The absorption of rosiglitazone is not affected by increases in gastric pH.

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 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.

Glimepiride
Absorption
After oral administration, glimepiride is completely (100%) absorbed from the gastrointestinal tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with type 2 diabetes mellitus have shown significant absorption of glimepiride within 1 h after administration and C_{max} at approximately 2.5 h. There is a linear relationship between dose and both C_{max} and AUC.

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

Metabolism
Glimepiride is completely metabolised by oxidative biotransformation after either an intravenous or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). CYP2C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolised to M2 by one or several cytosolic enzymes. M1, but not M2, possesses

about 1/3 of the pharmacological activity as compared to its parent in an animal model. The clinical significance of the glucose-lowering effect of M1 is unclear.

Elimination
The elimination half-life of glimepiride is approximately 5 to 8 h. When ^{14}C-glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in seven days and M1 (predominant) and M2 accounted for 80 to 90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in faeces and M1 and M2 (predominant) accounted for about 70% of that recovered in faeces. No parent drug was recovered from urine or faeces. After intravenous dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite was observed.

Special populations
Gender: In the pooled population pharmacokinetic analysis, there were no marked differences in the pharmacokinetics of rosiglitazone or glimepiride between males and females.

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

Hepatic impairment: Following rosiglitazone treatment 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. No adequate pharmacokinetic studies of glimepiride have been conducted in subjects with functional hepatic impairment. Therefore AVAGLIM should not be used in patients with hepatic impairment (see section 4.3)

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. There are no data from the use of glimepiride in patients on renal dialysis (see section 4.3).

A multiple-dose titration study with glimepiride conducted in 16 patients with type 2 diabetes mellitus with renal impairment using doses ranging from 1 to 8 mg daily for three months showed that all patients with a creatinine clearance less than 22 ml/min had adequate control of their glucose levels with a dosage regimen of only 1 mg daily (see section 4.2 and 4.4).

5.3 Preclinical safety data

No animal studies have been conducted with the combined products in AVAGLIM. The following data are findings in studies performed with rosiglitazone or glimepiride 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.

Glimepiride
Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use or were caused by the pharmacodynamic effect (hypoglycaemia) of the substance. This was based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and fertility. Studies on embryofoetal development and pre-and postnatal development revealed eye malformations, skeletal anomalies, abortions, and an increased foetal death rate.
Reproduction toxicology findings may be related to the pharmacodynamic action of glimepiride. Glimepiride is excreted into the milk of lactating rats. High doses given to mother rats cause hypoglycaemia in suckling young rats (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

4/4
Tablet core:
Sodium starch glycolate Type A
Hypromellose (E464)
Microcrystalline cellulose (E460)
Lactose monohydrate
Magnesium stearate.

Film coat:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400
Iron oxide black (E172)
Iron oxide red (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 blisters (PVC/PVDC/aluminium). Packs of 14, 28, 56, 84 or 112 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/1/06/349/001-004
EU/1/06/349/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 June 2006

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/

1. NAME OF THE MEDICINAL PRODUCT

AVAGLIM 8 mg/4 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains rosiglitazone maleate corresponding to 8 mg rosiglitazone and 4 mg glimepiride.

Excipient
- contains lactose (approximately 235 mg)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Red, biconvex, rounded triangular tablet with “gsk” debossed on one side and “8/4” on the other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AVAGLIM is indicated in the treatment of type 2 diabetes mellitus patients who are unable to achieve sufficient glycaemic control on optimal dosage of sulphonylurea monotherapy, and for whom metformin is inappropriate because of contraindication or intolerance.

4.2 Posology and method of administration

AVAGLIM therapy should be individualised for each patient. Before therapy is initiated with AVAGLIM appropriate clinical evaluation should be made to assess the patient’s risk of developing hypoglycaemia (see section 4.4).

AVAGLIM should be taken once daily shortly before or during a meal (usually the first main meal of the day). If a dose is forgotten, the following dose must not be increased.

For patients inadequately controlled on glimepiride monotherapy (typically 4 mg). Concomitant administration should be considered before the patient is switched to AVAGLIM. Where clinically appropriate, direct change from glimepiride monotherapy to AVAGLIM may be considered**.** The starting dose is 4 mg/day rosiglitazone plus 4 mg/day glimepiride (given as one tablet AVAGLIM 4 mg/4 mg).

Patients unable to achieve glycaemic control on at least half-maximum dose of other sulphonylurea monotherapy (except chlorpropamide, see section 4.4). Rosiglitazone 4 mg should be administered concomitantly with the dose of sulphonylurea already being taken. Once glycaemic control is stable at these doses, AVAGLIM may be introduced at a starting dose of 4 mg rosiglitazone/4 mg glimepiride once daily.

AVAGLIM may be used to substitute concomitant sulphonylurea and rosiglitazone in established dual oral therapy providing the patient has achieved at least half-maximum dose of sulphonylurea.

The dose of the rosiglitazone component can be increased after 8 weeks if required. The maximum recommended daily dose is 8 mg rosiglitazone/4 mg glimepiride (given as one AVAGLIM tablet 8 mg/4 mg, once daily). 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 4.4 and 4.8).

If hypoglycaemic symptoms occur, the patient should revert to concomitant therapy and adjust the glimepiride dose as appropriate.

Elderly
Due to the potential for decreased renal function the initiation and maintenance of therapy with AVAGLIM in elderly patients should be under close medical supervision due to an increased susceptibility to hypoglycaemia (see section 4.4).

Patients with renal impairment
Mild or moderate renal impairment (creatinine clearance 30 to 80 ml/min):
-Patients changing to AVAGLIM from sulphonylurea therapies other than glimepiride may be at an increased risk of hypoglycaemia (see section 4.4). Appropriate monitoring is advised.
AVAGLIM is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 ml/min, see section 4.3).

Patients with hepatic impairment
AVAGLIM is contraindicated in patients with hepatic impairment (see section 4.3).

Children and adolescents
AVAGLIM is not recommended for use in children below 18 years of age as there are no data available on its safety and efficacy.

4.3 Contraindications

Use of AVAGLIM is contraindicated in patients with:

- hypersensitivity to rosiglitazone, glimepiride, other sulphonylureas or sulphonamides 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
- severe renal impairment i.e. creatinine clearance less than 30 ml/min (including renal dialysis).
- insulin dependant diabetes
- diabetic ketoacidosis or diabetic coma.

4.4 Special warnings and precautions for use

AVAGLIM is not indicated for combination use with metformin and therefore should not be used in triple oral therapy of diabetes.

The following statements refer to AVAGLIM or the two individual active substances (rosiglitazone and glimepiride).

Hypoglycaemia
Patients receiving AVAGLIM may be at risk of dose-related hypoglycaemia (see section 4.8). It is advised that patients established on rosiglitazone and chlorpropamide concomitant therapy should not switch to AVAGLIM as chlorpropamide has a long half-life which may increase the risk of hypoglycaemia. If risk factors for hypoglycaemia are present (including renal insufficiency, low body weight, malnourishment, co-administration with certain other medicinal products (see section 4.5) or if the patient's life-style changes) it may be necessary to revert to concomitant therapy and down titrate the glimepiride dose. A switch to insulin should be considered in stress situations (e.g. trauma, surgery, infections).

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 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. 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 with rosiglitazone (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 AVAGLIM in all patients and periodically thereafter based on clinical judgement. Therapy with AVAGLIM 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 AVAGLIM 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.

Patients with renal impairment
Patients with mild or moderate renal impairment (creatinine clearance 30 to 80 ml/min) may be at an increased risk of hypoglycaemia (see sections 4.2, 4.3 and 4.4). Appropriate monitoring is advised.

Premenopausal anovulatory women
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).

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.

Haematological monitoring
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 AVAGLIM.

Periodic haematological monitoring (especially leucocytes and thrombocytes) are required during treatment with AVAGLIM.

Treatment of patients with G6PD-deficiency with sulphonylurea agents can lead to haemolytic anaemia. Since glimepiride belongs to the chemical class of sulphonylurea drugs, caution should be used in patients with G6PD-deficiency and a non-sulphonylurea alternative should be considered.

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.

Administration with other medicinal products
Rosiglitazone should be used with caution during concomitant administration of CYP2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin). Glimepiride should be used with caution during concomitant administration of CYP2C9 inhibitors (e.g. fluconazole) or inducers (see section 4.5). Glycaemic control should be monitored closely. AVAGLIM dose adjustment within the recommended posology or changes in diabetic treatment should be considered.

Lactose intolerance
AVAGLIM 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 AVAGLIM. 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 glimepiride).

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

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

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).

Concomitant administration of rosiglitazone with the oral anti-diabetic agents metformin, glimepiride, 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.

Glimepiride
If glimepiride is taken simultaneously with certain other medicines, both undesired increases and decreases in the hypoglycaemic action of glimepiride can occur. For this reason, other medicines should only be taken with the knowledge (or at the prescription) of the doctor.

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole

Results from an vivo interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.

Based on the experience with glimepiride and with other sulphonylureas the following interactions have to be mentioned.

Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following drugs is taken, for example:

phenylbutazone, azapropazon and oxyfenbutazone,
insulin and oral antidiabetic products,
metformin,
salicylates and p-amino-salicylic acid,
anabolic steroids and male sex hormones,
chloramphenicol,
coumarin anticoagulants,
fenfluramine,
fibrates,
ACE inhibitors,
fluoxetine,
allopurinol,
sympatholytics,
cyclo-, tro-and iphosphamides,
sulphinpyrazone,
certain long acting sulphonamides,
tetracyclines,
MAO-inhibitors,
quinolone antibiotics,
probenecid,
miconazol,
pentoxifylline (high dose parenteral),
tritoqualine,
fluconazole.

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following drugs is taken, for example:

oestrogens and progestagens,
saluretics, thiazide diuretics,
thyroid stimulating agents, glucocorticoids,
phenothiazine derivatives, chlorpromazine,
adrenaline and sympathicomimetics,
nicotinic acid (high dosages) and nicotinic acid derivatives,
laxatives (long term use),
phenytoin, diazoxide,
glucagon, barbiturates and rifampicin,
acetozolamide.

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

Under the influence of sympatholytic drugs such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counterregulation to hypoglycaemia may be reduced or absent.

Alcohol intake may potentiate or weaken the hypoglycaemic action of glimepiride in an unpredictable fashion.

Glimepiride may either potentiate or weaken the effects of coumarin derivatives.

4.6 Pregnancy and lactation

For AVAGLIM 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 either active substance (rosiglitazone and glimepiride) in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Therefore, AVAGLIM should not be used during pregnancy and the use of insulin is recommended. If a patient wishes to become pregnant or if pregnancy occurs, treatment with AVAGLIM should be discontinued.

Both rosiglitazone and glimepiride have been detected in the milk of experimental animals. It is not known whether breast-feeding will lead to exposure of the infant to medicinal product. Therefore, AVAGLIM should not be used during lactation.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. Nevertheless, the potential for hypoglycaemia should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills (e.g. driving).

4.8 Undesirable effects

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

AVAGLIM
Data from double-blind studies confirm that the safety profile of concomitant rosiglitazone and glimepiride is similar to that of the combined adverse reaction profile for the two active substances. Limited data with AVAGLIM is also consistent with this combined adverse reaction profile.

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. 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 with rosiglitazone

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

*The frequency category for the background incidence of this event, 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 or dual 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 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 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. marketing experience. In very rare cases a fatal outcome has been reported.

Glimepiride

Clinical trial data and post-marketing data
Table 3 presents adverse reactions by system organ class and by frequency category based on experience with glimepiride and other sulphonylureas. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥1/10,000, <1/1000) and very rare (<1/10,000 including isolated reports).

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

Adverse reaction	Frequency
Blood and lymphatic system disorders	
agranulocytosis	Rare
granulocytopenia	Rare
pancytopenia	Rare
haemolytic anaemia	Rare
thrombocytopenia	Rare
leukopenia	Rare
erythrocytopenia	Rare
Immune system disorders[6]	
allergic vasculitis	Very rare
hypersensitivity reactions[7]	Very rare
Metabolism and nutrition disorders	
hypoglycaemia[8]	Very common

Gastrointestinal disorders	
vomiting	Very rare
diarrhoea	Very rare
nausea	Very rare
abdominal distension	Very rare
abdominal pain	Very rare
abdominal discomfort	Very rare
Hepatobiliary disorders[9]	
hepatitis[10]	Very rare
impairment of liver function (e.g. with cholestasis and jaundice)	Very rare
Skin and subcutaneous tissue disorders[11]	
hypersensitivity of the skin to light	Very rare
Investigations	
serum sodium decrease	Very rare

[6] Cross-allergenicity with sulphonylureas, sulphonamides or related substances is possible.
[7] Mild hypersensitivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock.

[8] Based on what is known of other sulphonylureas, hypoglycaemia may be prolonged. Rarely hypoglycaemic reactions can occur immediately and may be severe and not always easy to correct.

[9] Elevation of liver enzymes may occur.
[10] Hepatitis may progress to liver failure.

[11] Hypersensitivity reactions of the skin may occuras itching, rash and urticaria.

Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.

4.9 Overdose

No data are available with regard to overdose of AVAGLIM.

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.

Overdose of sulphonylureas, including glimepiride, can result in severe life-threatening hypoglycaemia lasting 12 to 72 hours, which may recur after apparent recovery. The symptoms may be delayed for up to 24 hours after ingestion. Hospitalisation should be considered as appropriate.

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 and glimepiride are both highly protein bound and would not be expected to be cleared by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of oral blood glucose lowering drugs, ATC code: A10BD04

AVAGLIM combines two antidiabetic 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 glimepiride, a member of the sulphonylurea class. Thiazolidinediones act primarily by reducing insulin resistance and sulphonylureas act primarily by stimulating release of insulin from functioning pancreatic β-cells. A study comparing AVAGLIM to monotherapy rosiglitazone or glimepiride demonstrated incremental benefit in control of glycaemia of the fixed-dose combination over monotherapy. No new safety findings were observed. The clinical trial program in support of this fixed dose combination only compared rosiglitazone and glimepiride to glimepiride monotherapy and not to monotherapy with other sulphonylureas.

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 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.

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.

Glimepiride
Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group. It may be used in non-insulin dependent diabetes mellitus.
Glimepiride acts mainly by stimulating the release of insulin from the beta cells of the pancreas. As with other sulphonylureas, this effect is based on an improvement in responsiveness of pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects, also postulated for other sulphonylureas.

Sulphonylureas regulate insulin secretion by closing the ATP-dependent potassium channels in the beta cell membrane. Closure of the potassium channels leads to depolarisation of the beta cell and results by opening of the calcium channels – to an increased influx of calcium into the cell. This leads to a release of insulin by exocytosis.

Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel but which differs from the usual sulphonylurea binding site.

Extrapancreatic effects include an improvement in insulin sensitivity of peripheral tissue and a reduction in hepatic uptake of insulin.
Glimepiride very rapidly increases the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulation of glucose uptake.
Glimepiride increases the activity of glycosyl-phosphatidylinositol-specific phospholipase C, which may be associated with drug-induced lipogenesis and glycogenesis in isolated fat and muscle cells.
Glimepiride inhibits the hepatic glucose production by increasing the intracellular concentration of fructose-2,6 bisphosphate, which in turn inhibits gluconeogenesis.

The minimum effective oral dose is approximately 0.6 mg. The effect of glimepiride is dose-dependent and reproducible. The physiological response to acute physical exercise, a reduction in insulin secretion, is maintained during treatment with glimepiride.
There was no significant difference in the effect regardless of whether the drug was taken 30 minutes before or immediately before a meal. In diabetic patients, good metabolic control over 24 hours can be achieved with a single daily dose.
Although the hydroxy metabolite of glimepiride caused a small but significant reduction in serum glucose, it accounts for only a minor part of the total drug effect.

5.2 Pharmacokinetic properties

AVAGLIM

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

In a bioequivalence study under fasted conditions, the AUC and C_{max} of rosiglitazone and the AUC of glimepiride following a single dose of a 4 mg/4 mg combination tablet were bioequivalent to concomitant administration of rosiglitazone 4 mg and glimepiride 4 mg.

In the fed state, the rate and extent of absorption of the rosiglitazone-glimepiride 4 mg/4 mg combination were equivalent to concomitant administration of 4 mg rosiglitazone and 4 mg glimepiride. Administration of the 4 mg/4 mg combination with food led to an increase in glimepiride exposure compared to that observed on administration in the fasted state. Glimepiride AUC_{0-t}, AUC_{0-inf} and C_{max} were increased by 30%, 19% and 55% respectively, on average. For rosiglitazone, C_{max} values were decreased by approximately 32% with food.

The AUC and C_{max} of glimepiride increased in a dose-proportional manner following administration of rosiglitazone-glimepiride 4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg.

The following statements reflect the pharmacokinetic properties of the individual components of AVAGLIM.

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 fasted state. These small changes are not clinically significant and, therefore, it is not necessary to administer rosiglitazone at any particular time in relation to meals. The absorption of rosiglitazone is not affected by increases in gastric pH.

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 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.

Glimepiride
Absorption
After oral administration, glimepiride is completely (100%) absorbed from the gastrointestinal tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with type 2 diabetes mellitus have shown significant absorption of glimepiride within 1 h after administration and C_{max} at approximately 2.5 h. There is a linear relationship between dose and both C_{max} and AUC.

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

Metabolism
Glimepiride is completely metabolised by oxidative biotransformation after either an intravenous or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). CYP2C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolised to M2 by one or several cytosolic enzymes. M1, but not M2, possesses

about 1/3 of the pharmacological activity as compared to its parent in an animal model. The clinical significance of the glucose-lowering effect of M1 is unclear.

Elimination
The elimination half-life of glimepiride is approximately 5 to 8 h. When ^{14}C-glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in seven days and M1 (predominant) and M2 accounted for 80 to 90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in faeces and M1 and M2 (predominant) accounted for about 70% of that recovered in faeces. No parent drug was recovered from urine or faeces. After intravenous dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite was observed.

Special populations
Gender: In the pooled population pharmacokinetic analysis, there were no marked differences in the pharmacokinetics of rosiglitazone or glimepiride between males and females.

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

Hepatic impairment: Following rosiglitazone treatment 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. No adequate pharmacokinetic studies of glimepiride have been conducted in subjects with functional hepatic impairment. Therefore AVAGLIM should not be used in patients with hepatic impairment (see section 4.3)

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. There are no data from the use of glimepiride in patients on renal dialysis (see section 4.3).

A multiple-dose titration study with glimepiride conducted in 16 patients with type 2 diabetes mellitus with renal impairment using doses ranging from 1 to 8 mg daily for three months showed that all patients with a creatinine clearance less than 22 ml/min had adequate control of their glucose levels with a dosage regimen of only 1 mg daily (see section 4.2 and 4.4).

5.3 Preclinical safety data

No animal studies have been conducted with the combined products in AVAGLIM. The following data are findings in studies performed with rosiglitazone or glimepiride 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.

Glimepiride
Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use or were caused by the pharmacodynamic effect (hypoglycaemia) of the substance. This was based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and fertility. Studies on embryofoetal development and pre-and postnatal development revealed eye malformations, skeletal anomalies, abortions, and an increased foetal death rate.
Reproduction toxicology findings may be related to the pharmacodynamic action of glimepiride. Glimepiride is excreted into the milk of lactating rats. High doses given to mother rats cause hypoglycaemia in suckling young rats (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

8/4
Tablet core:
Sodium starch glycolate Type A
Hypromellose (E464)
Microcrystalline cellulose (E460)
Lactose monohydrate
Magnesium stearate.

Film coat:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400
Iron oxide red (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 blisters (PVC/PVDC/aluminium). Packs of 14, 28, 56, 84 or 112 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/1/06/349/005-008
EU/1/06/349/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 June 2006

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/

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer 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 aplicable.

- **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 MAH 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 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, any updated RMP should be submitted at the same time as the following 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
- At the request of the EMEA.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

AVAGLIM 4 mg/4 mg film-coated tablets.
rosiglitazone/glimepiride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rosiglitazone maleate corresponding to 4 mg rosiglitazone and 4 mg glimepiride.

3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablets

14 tablets
28 tablets
56 tablets
84 tablets
112 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 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/1/06/349/001 14 tablets
EU/1/06/349/002 28 tablets
EU/1/06/349/003 56 tablets
EU/1/06/349/004 112 tablets
EU/1/06/349/009 84 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

AVAGLIM 4 mg/4 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

AVAGLIM 4 mg/4 mg film-coated tablets.
rosiglitazone/glimepiride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

AVAGLIM 8 mg/4 mg film-coated tablets.
rosiglitazone/glimepiride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rosiglitazone maleate corresponding to 8 mg rosiglitazone and 4 mg glimepiride.

3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablets

14 tablets
28 tablets
56 tablets
84 tablets
112 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 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/1/06/349/005 14 tablets
EU/1/06/349/006 28 tablets
EU/1/06/349/007 56 tablets
EU/1/06/349/008 112 tablets
EU/1/06/349/010 84 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

AVAGLIM 8 mg/4 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

AVAGLIM 8 mg/4 mg film-coated tablets.
rosiglitazone/glimepiride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

AVAGLIM 4 mg/4 mg film-coated tablets
AVAGLIM 8 mg/4 mg film-coated tablets
rosiglitazone/glimepiride

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 AVAGLIM IS AND WHAT IT IS USED FOR

Avaglim tablets are a combination of two different medicines called *rosiglitazone* and *glimepiride.* 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 glimepiride work together so your body makes better use of the insulin it produces, and this helps reduce your blood sugar to a normal level.

2. BEFORE YOU TAKE AVAGLIM

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

Don't take Avaglim:
- **if you are allergic** (*hypersensitive*) to rosiglitazone, glimepiride, or any of the other ingredients of Avaglim (*listed in Section 6),* or to other medicines called sulphonylureas (like *glibenclamide*) or sulphonamides
- **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 liver disease**
- **if you have had diabetic ketoacidosis** (a complication of diabetes causing rapid weight loss, nausea or vomiting)
- **if you have severe kidney disease**
- **if you have type 1 diabetes** – this needs different treatment.

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

Take special care with Avaglim

Avaglim 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 Avaglim may not be suitable for you.

Haemolytic anaemia: If you have an inherited condition where your red blood cells don't produce enough of the enzyme G6PD, Avaglim may cause your red blood cells to be destroyed too quickly (*haemolytic anaemia*).

➔ **Tell your doctor** if you have this condition, as Avaglim may not be suitable for you.

Conditions to look out for

Avaglim 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 Avaglim, 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 Avaglim. 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).*

You will have regular blood tests

Avaglim can cause reductions in some types of blood cells. Your doctor should regularly test your blood while you are taking Avaglim.

Your kidney function will be checked

If you have kidney disease, or are over 65, your kidney function should be checked while you are taking Avaglim.

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.

Many medicines (or alcohol) can affect the way Avaglim controls the amount of sugar in your blood. Your blood sugar levels may become too high or too low (*see 'Low blood sugar' in Section 4*). Some of the medicines most likely to do this are:

- gemfibrozil (used to **lower cholesterol**)
- rifampicin (used to treat **tuberculosis** and other infections)
- fluconazole (used to treat **fungal infections**).

➔ **Tell a doctor or pharmacist** if you think that Avaglim is not working as it should, particularly if you are taking any other medicines. You may need to have the dose adjusted or change the other medicines you are taking.

Some medicines used to treat **high blood pressure** (such as beta-blockers, clonidine, guanethidine or reserpine) may make you less aware of the warning signs of low blood sugar (sweating; fast irregular heartbeats).

➔ **Checking your blood sugar levels** regularly is especially important if you are taking any of these medicines, **even if you are feeling well**

Avaglim can also strengthen or weaken the effects of medicines to **prevent blood clots** (anticoagulants such as warfarin).

➔ **Tell your doctor or pharmacist** if you are taking anticoagulants**.**

Pregnancy and breast-feeding

- **Avaglim is not recommended during pregnancy.** If you are pregnant or could be pregnant, tell your doctor.

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

Driving and using machines
Avaglim can make you dizzy or cause your blood sugar to become lower than normal (*see 'Low blood sugar' in Section 4*).
➔ **Don't drive or operate machinery** unless you're feeling well.

Avaglim contains lactose
Avaglim 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 AVAGLIM

Always take Avaglim 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 (4 mg rosiglitazone and 4 mg glimepiride), taken once a day.

After about 8 weeks your doctor may need to increase your dose. The maximum dose is one combined tablet of 8 mg rosiglitazone and 4 mg glimepiride, taken once a day.

How to take
Swallow the tablets with some water.

It is best to take Avaglim with food, or just before food, usually with your first main meal of the day.

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

If you take more Avaglim than you should
If you accidentally take too many tablets, contact your doctor or pharmacist for advice. You may be at risk of having low blood sugar and need hospital treatment.

If you forget to take Avaglim
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 Avaglim
Take Avaglim for as long as your doctor recommends. If you stop taking Avaglim, 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, Avaglim 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 Avaglim. 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 Avaglim.**

Fluid retention and heart failure: Avaglim 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*): Certain conditions can make you more likely to suffer from low blood sugar while you are taking Avaglim. These include:
- taking other medicines to treat diabetes
- kidney disease
- low body weight or poor diet
- stress situations (such as trauma, surgery or infections)

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 Avaglim 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
- 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 Avaglim 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:
- lower blood sugar than normal (*hypoglycaemia*)
- swelling (*oedema)* due to water retention.

Common side effects
These may affect **up to 1 in 10** people:
- chest pain (*angina*)
- heart failure
- broken bones
- increased weight, increased appetite
- dizziness
- constipation
- reduction in blood count (*anaemia*) low numbers of white blood cells (*leucopaenia*) and blood cells needed for blood clotting (*thrombocytopaenia*)
- small increases in blood cholesterol, increased amount of fats in the blood

Rare side effects
These may affect **up to 1 in 1,000** people:
- fluid in the lungs (*pulmonary oedema*) causing breathlessness
- swelling of the retina at the back of the eye (*macular oedema*)
- reduction in the number of red blood cells, or a type of white blood cell (*granulocytopaenia*) which can be severe (*agranulocytosis*), reduction in the number of all types of blood cells (*pancytopaenia*)
- 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 blood vessels (*allergic vasculitis*)
- increased sensitivity to the sun causing skin rash
- inflammation of the liver (*hepatitis*), yellowing of the skin (*jaundice*)
- rapid and excessive weight gain caused by fluid retention
- stomach pain, bloating, feeling sick (*nausea*), vomiting or diarrhoea
- decrease in the amount of sodium in your 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 AVAGLIM

Keep out of the reach and sight of children.

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

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 Avaglim contains
The active substances are rosiglitazone and glimepiride. Avaglim tablets come in different strengths. Each tablet contains either: 4 mg or 8 mg rosiglitazone and 4 mg glimepiride.

The other ingredients are: sodium starch glycollate (Type A), hypromellose (E464), microcrystalline cellulose (E460), lactose monohydrate, magnesium stearate, titanium dioxide (E171), macrogol 400, iron oxide black and/or red (E172).

What Avaglim looks like and contents of the pack
Avaglim 4 mg/4 mg tablets are pink, rounded triangular-shaped, and marked "gsk" on one side and "4/4" on the other.

Avaglim 8 mg/4 mg tablets are red, rounded triangular-shaped, and marked "gsk" on one side and "8/4" on the other.

The tablets are supplied in blister packs containing 14, 28, 56, 84 or 112 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.

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

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

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

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

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

Malta
GlaxoSmithKline Malta
Tel: + 356 21 238131

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ísland
GlaxoSmithKline ehf.
Sími: + 354 530 3700

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

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/
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