ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 1 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains rosiglitazone maleate corresponding to 1 mg rosiglitazone.

For excipients see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

Yellow film-coated tablets marked "SB" on one side and "1" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rosiglitazone is indicated only in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea:

– in combination with metformin only in obese patients.
– in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated.
4.2 Posology and method of administration

Treatment should only be initiated by a physician experienced in the treatment of type 2 diabetes.

Experience from clinical trials with rosiglitazone is currently limited to 2 years. The long-term benefits of therapy with rosiglitazone have not been demonstrated (see section 5.1).

Rosiglitazone therapy is usually initiated at 4 mg/day.

Combination with Metformin

This dose can be increased to 8 mg/day after 8 weeks if greater glycaemic control is required.

Combination with sulphonylurea

There is currently no experience with doses of rosiglitazone above 4 mg/day in combination with sulphonylureas.

Rosiglitazone may be given once or twice a day.

Rosiglitazone may be taken with or without food.

Elderly

No dose adjustment is required in the elderly.

Patients with renal impairment

No dose adjustment is required in patients with mild and moderate renal insufficiency. Rosiglitazone should not be used in patients with severe renal insufficiency.
Patients with hepatic impairment

Rosiglitazone should not be used in patients with hepatic impairment.

Children and adolescents

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

4.3 Contraindications

Use of rosiglitazone is contraindicated in patients with:

- known hypersensitivity to rosiglitazone or to any of the excipients of the tablet, or

- cardiac failure or history of cardiac failure (NYHA stages I to IV), or

- hepatic impairment.

Rosiglitazone is also contraindicated for use in combination with insulin.

4.4 Special warnings and special precautions for use

There is no clinical experience with rosiglitazone in triple combination with other oral anti-diabetic anti-diabetics.

Rosiglitazone should not be used in monotherapy.

Fluid retention and cardiac failure

Rosiglitazone, can cause fluid retention which may exacerbate or precipitate heart failure. Patients should be observed for signs and symptoms of heart failure, particularly those with reduced cardiac reserve. Rosiglitazone should be discontinued if any deterioration in cardiac status occurs. An increased incidence of cardiac failure has been observed in clinical trials when rosiglitazone is used in combination with insulin. Therefore rosiglitazone is
contraindicated in combination with insulin. Heart failure was also reported more frequently in patients with a history of heart failure, in elderly patients and in patients with mild or moderate renal failure. Since NSAIDs and rosiglitazone are associated with fluid retention, concomitant administration may increase the risk of oedema.

**Monitoring of liver function**

There have been rare reports of hepatocellular dysfunction during post-marketing experience (see section 4.8). It is recommended, therefore, that patients treated with rosiglitazone undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with rosiglitazone in all patients. Therapy with rosiglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal) or with any other evidence of liver disease. Following initiation of therapy with rosiglitazone, it is recommended that liver enzymes be monitored every two months for the first twelve months, and periodically thereafter. If ALT levels are increased to >3X upper limit of normal during rosiglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with rosiglitazone should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

**Weight gain**

In clinical trials with rosiglitazone there was evidence of weight gain, therefore weight should be closely monitored.
Anaemia

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

Others

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

Rosiglitazone has not been studied in patients with severe renal impairment and is therefore not recommended in these patients.

Caution should be used when administering paclitaxel and rosiglitazone concomitantly (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

*In vitro* studies demonstrate that rosiglitazone is predominantly metabolised by CYP2C8, with CYP2C9 as only a minor pathway. No *in vivo* interaction studies have been performed with CYP2C8 substrates (e.g. cerivastatin and paclitaxel). The potential for a clinically relevant interaction with cerivastatin is considered to be low. Although rosiglitazone is not anticipated to affect the pharmacokinetics of paclitaxel, concomitant use is likely to result in inhibition of the metabolism of rosiglitazone. Therefore caution should be used during concomitant administration with paclitaxel. Clinically significant interactions with CYP2C9 substrates or inhibitors are not anticipated.

Concomitant administration with the oral anti-diabetic agents metformin, glibenclamide and acarbose did not result in any clinically relevant pharmacokinetic interactions with rosiglitazone. Moderate ingestion of alcohol with rosiglitazone has no effect on glycaemic control.
No clinically relevant interactions with digoxin, the CYP2C9 substrate warfarin, the CYP3A4 substrates nifedipine, ethinylestradiol or norethindrone were observed after co-administration with rosiglitazone.

4.6 Pregnancy and lactation

There are no adequate data of the use of rosiglitazone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Rosiglitazone should not be used during pregnancy.

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

4.7 Effects on ability to drive and use machines

No effects on the ability to drive or operate machinery have been observed.

4.8 Undesirable effects

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

**ROSIGLITAZONE IN COMBINATION WITH METFORMIN**

**Red Blood Cell**

Common: anaemia.

**Metabolism and Nutritional**

Common: hypoglycaemia, hyperglycaemia.
Uncommon: hyperlipaemia, acidosis lactic, diabetes mellitus aggravated, hypercholesterolaemia.

**Central and Peripheral Nervous System**
Common: headache.
Uncommon: dizziness.

**Gastrointestinal System**
Common: diarrhoea, flatulence, nausea, abdominal pain, dyspepsia.
Uncommon: vomiting, anorexia, constipation.

**Body as a Whole General**
Common: fatigue.

**ROSIGLITAZONE IN COMBINATION WITH SULPHONYLUREA**

**Red blood cell**
Uncommon: anaemia.

**Platelet Bleeding and Clotting**
Uncommon: thrombocytopenia.

**Metabolism and Nutritional**
Common: hypoglycaemia, hyperglycaemia, weight increase.
Uncommon: hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia.

**Psychiatric**
Uncommon: somnolence.
Central and Peripheral Nervous System
Uncommon: dizziness, headache, paresthesia.

Respiratory
Uncommon: dyspnea.

Gastrointestinal
Uncommon: abdominal pain, flatulence, nausea, appetite increased.

Skin and appendages
Uncommon: alopecia, rash.

Body as a whole general
Uncommon: fatigue, asthenia.

In double blind studies, oedema occurred in 3.0% of patients treated with rosiglitazone + sulphonylurea and in 4.4% of patients treated with rosiglitazone + metformin. The incidence of anaemia was higher when rosiglitazone was used in combination with metformin. Adverse experiences of hypercholesterolaemia were reported in 3.6% and 2.1% of patients treated with rosiglitazone + sulphonylurea and rosiglitazone + metformin respectively. 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.

In 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 also low (0.6% rosiglitazone + sulphonylurea; 0.5% rosiglitazone + metformin) compared to an incidence of 0.7% for placebo. Isolated cases of elevated liver enzymes and hepatocellular dysfunction have occurred in post-marketing experience. Although in very rare cases fatal outcome has been reported, causal relationship has not been established.

Heart failure occurred uncommonly during double-blind clinical studies of rosiglitazone in combination with SU (0.6%) or metformin (0.3%) but was reported with a four-fold higher incidence during studies of rosiglitazone in combination with insulin (2.5%).
In 24 month studies, rosiglitazone treatment was associated with a mean increase of 3.7% in weight in combination with metformin and a mean increase of 6.3% in combination with SU.

4.9 **Overdose**

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

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

5. **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

**Pharmacotherapeutic group: antihyperglycaemic, ATC code: A10 BG 02**

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

**Preclinical data**

The antihyperglycaemic activity of rosiglitazone has been demonstrated in a number of animal models of type 2 diabetes. In addition, rosiglitazone preserved \(\beta\)-cell function as shown by increased pancreatic islet mass and insulin content and prevented the development of overt hyperglycaemia in animal models of type 2 diabetes. Rosiglitazone did not stimulate pancreatic insulin secretion or induce hypoglycaemia in rats and mice. The major metabolite (para-hydroxy-sulphate) with high affinity to the soluble human PPAR\(\gamma\), exhibited relatively high potency in a glucose tolerance assay in obese mouse. The clinical relevance of this observation has not been fully elucidated.
Clinical trials data

The glucose lowering effects observed with rosiglitazone are gradual in onset with near maximal reductions in fasting plasma glucose (FPG) evident following approximately 8 weeks of therapy. Rosiglitazone was associated with increases in weight.

Consistent with the mechanism of action of rosiglitazone, results from a homeostatic model assessment (HOMA) indicate reduced insulin resistance and improved pancreatic β-cell function with rosiglitazone in combination with sulphonylurea or metformin. Improved glycaemic control was also associated with significant decreases in free fatty acids. As a consequence of different but complementary mechanisms of action, combination therapy of rosiglitazone with a sulphonylurea or metformin resulted in additive effects on glycaemic control in type 2 diabetic patients.

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

The efficacy of rosiglitazone in combination with SU or metformin has not been compared to the combination of SU plus metformin. There are no studies assessing long-term cardiovascular outcome in patients receiving rosiglitazone in combination with a sulphonylurea or metformin.

5.2 Pharmacokinetic properties

Absorption:

Absolute bioavailability of rosiglitazone following both a 4 and an 8 mg oral dose is approximately 99%. Rosiglitazone plasma concentrations peak at around 1 hour after dosing. Plasma concentrations are approximately dose proportional over the therapeutic dose range.

Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), although a small decrease in $C_{\text{max}}$ (approx 20-28%) and a delay in $t_{\text{max}}$ (ca.1.75 h) were observed compared to dosing in the fasting state. These small changes are not clinically significant and, therefore, it is not necessary to administer rosiglitazone at any particular time in relation to meals. The absorption of rosiglitazone is not affected by increases in gastric pH.

Distribution:
The volume of distribution of rosiglitazone is approximately 14 litres in healthy volunteers. Plasma protein binding of rosiglitazone is high (approximately 99.8%) and is not influenced by concentration or age. The protein binding of the major metabolite (para-hydroxy-sulphate) is very high (>99.9%).

Metabolism:

Metabolism of rosiglitazone is extensive with no parent compound being excreted unchanged. The major routes of metabolism are N-demethylation and hydroxylation, followed by conjugation with sulphate and glucuronic acid. The contribution of the major metabolite (para-hydroxy-sulphate) to the overall anti-diabetic activity of rosiglitazone has not been fully elucidated in man and it cannot be ruled out that the metabolite may contribute to the activity. However, this raises no safety concern regarding target or special populations as hepatic impairment is contraindicated and the phase III clinical studies included a considerable number of elderly patients and patients with mild to moderate renal impairment.

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

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

Elimination:

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

Special populations:

Gender: In the pooled population pharmacokinetic analysis, there were no marked differences in the pharmacokinetics of rosiglitazone between males and females.
Elderly: In the pooled population pharmacokinetic analysis, age was not found to influence the pharmacokinetics of rosiglitazone to any significant extent.

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

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

5.3 Preclinical safety data

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

**Film coating:**
Opadry yellow OY-L-22809 (hypromellose 6cP, titanium dioxide E171, macrogol 3000, lactose monohydrate, glycerol triacetate, iron oxide yellow E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and content of container

Opaque blister packs (PVC/ aluminium). 56 film-coated tablets.

6.6 Instructions for use and handling, and disposal (if appropriate)

No special requirements.

7. MARKETING AUTHORISATION HOLDER
8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 2 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains rosiglitazone maleate corresponding to 2 mg rosiglitazone.

For excipients see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

Pink film-coated tablets marked "SB" on one side and "2" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rosiglitazone is indicated only in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea:

− in combination with metformin only in obese patients.
− in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated.
4.2 Posology and method of administration

Treatment should only be initiated by a physician experienced in the treatment of type 2 diabetes.

Experience from clinical trials with rosiglitazone is currently limited to 2 years. The long-term benefits of therapy with rosiglitazone have not been demonstrated (see section 5.1).

Rosiglitazone therapy is usually initiated at 4 mg/day.

Combination with Metformin

This dose can be increased to 8 mg/day after 8 weeks if greater glycaemic control is required.

Combination with sulphonylurea

There is currently no experience with doses of rosiglitazone above 4 mg/day in combination with sulphonylureas.

Rosiglitazone may be given once or twice a day.

Rosiglitazone may be taken with or without food.

Elderly

No dose adjustment is required in the elderly.

Patients with renal impairment

No dose adjustment is required in patients with mild and moderate renal insufficiency. Rosiglitazone should not be used in patients with severe renal insufficiency.
Patients with hepatic impairment

Rosiglitazone should not be used in patients with hepatic impairment.

Children and adolescents

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

4.3 Contraindications

Use of rosiglitazone is contraindicated in patients with:

- known hypersensitivity to rosiglitazone or to any of the excipients of the tablet, or

- cardiac failure or history of cardiac failure (NYHA stages I to IV), or

- hepatic impairment.

Rosiglitazone is also contraindicated for use in combination with insulin.

4.4 Special warnings and special precautions for use

There is no clinical experience with rosiglitazone in triple combination with other oral anti-diabetic anti-diabetics.

Rosiglitazone should not be used in monotherapy.

Fluid retention and cardiac failure

Rosiglitazone, can cause fluid retention which may exacerbate or precipitate heart failure. Patients should be observed for signs and symptoms of heart failure, particularly those with reduced cardiac reserve. Rosiglitazone should be discontinued if any deterioration in cardiac
status occurs. An increased incidence of cardiac failure has been observed in clinical trials when rosiglitazone is used in combination with insulin. Therefore rosiglitazone is contraindicated in combination with insulin. Heart failure was also reported more frequently in patients with a history of heart failure, in elderly patients and in patients with mild or moderate renal failure. Since NSAIDs and rosiglitazone are associated with fluid retention, concomitant administration may increase the risk of oedema.

**Monitoring of liver function**

There have been rare reports of hepatocellular dysfunction during post-marketing experience (see section 4.8). It is recommended, therefore, that patients treated with rosiglitazone undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with rosiglitazone in all patients. Therapy with rosiglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal) or with any other evidence of liver disease. Following initiation of therapy with rosiglitazone, it is recommended that liver enzymes be monitored every two months for the first twelve months, and periodically thereafter. If ALT levels are increased to >3X upper limit of normal during rosiglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with rosiglitazone should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

**Weight gain**

In clinical trials with rosiglitazone there was evidence of weight gain, therefore weight should be closely monitored.
Anaemia

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

Others

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

Rosiglitazone has not been studied in patients with severe renal impairment and is therefore not recommended in these patients.

Caution should be used when administering paclitaxel and rosiglitazone concomitantly (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

*In vitro* studies demonstrate that rosiglitazone is predominantly metabolised by CYP2C8, with CYP2C9 as only a minor pathway. *No in vivo* interaction studies have been performed with CYP2C8 substrates (e.g. cerivastatin and paclitaxel). The potential for a clinically relevant interaction with cerivastatin is considered to be low. Although rosiglitazone is not anticipated to affect the pharmacokinetics of paclitaxel, concomitant use is likely to result in inhibition of the metabolism of rosiglitazone. Therefore caution should be used during concomitant administration with paclitaxel. Clinically significant interactions with CYP2C9 substrates or inhibitors are not anticipated.

Concomitant administration with the oral anti-diabetic agents metformin, glibenclamide and acarbose did not result in any clinically relevant pharmacokinetic interactions with rosiglitazone. Moderate ingestion of alcohol with rosiglitazone has no effect on glycaemic control.
No clinically relevant interactions with digoxin, the CYP2C9 substrate warfarin, the CYP3A4 substrates nifedipine, ethinylestradiol or norethindrone were observed after co-administration with rosiglitazone.

4.6 Pregnancy and lactation

There are no adequate data of the use of rosiglitazone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Rosiglitazone should not be used during pregnancy.

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

4.7 Effects on ability to drive and use machines

No effects on the ability to drive or operate machinery have been observed.

4.8 Undesirable effects

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

**ROSIGLITAZONE IN COMBINATION WITH METFORMIN**

**Red Blood Cell**

Common: anaemia.

**Metabolism and Nutritional**

Common: hypoglycaemia, hyperglycaemia.
Uncommon: hyperlipaemia, acidosis lactic, diabetes mellitus aggravated, hypercholesterolaemia.

**Central and Peripheral Nervous System**

Common: headache.

Uncommon: dizziness.

**Gastrointestinal System**

Common: diarrhoea, flatulence, nausea, abdominal pain, dyspepsia.

Uncommon: vomiting, anorexia, constipation.

**Body as a Whole General**

Common: fatigue.

**ROSIGLITAZONE IN COMBINATION WITH SULPHONYLUREA**

**Red blood cell**

Uncommon: anaemia.

**Platelet Bleeding and Clotting**

Uncommon: thrombocytopenia.

**Metabolism and Nutritional**

Common: hypoglycaemia, hyperglycaemia, weight increase.

Uncommon: hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia.

**Psychiatric**

Uncommon: somnolence.
Central and Peripheral Nervous System
Uncommon: dizziness, headache, paresthesia.

Respiratory
Uncommon: dyspnea.

Gastrointestinal
Uncommon: abdominal pain, flatulence, nausea, appetite increased.

Skin and appendages
Uncommon: alopecia, rash.

Body as a whole general
Uncommon: fatigue, asthenia.

In double blind studies, oedema occurred in 3.0% of patients treated with rosiglitazone + sulphonylurea and in 4.4% of patients treated with rosiglitazone + metformin. The incidence of anaemia was higher when rosiglitazone was used in combination with metformin. Adverse experiences of hypercholesterolaemia were reported in 3.6% and 2.1% of patients treated with rosiglitazone + sulphonylurea and rosiglitazone + metformin respectively. 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.

In 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 also low (0.6% rosiglitazone + sulphonylurea; 0.5% rosiglitazone + metformin) compared to an incidence of 0.7% for placebo. Isolated cases of elevated liver enzymes and hepatocellular dysfunction have occurred in post-marketing experience. Although in very rare cases fatal outcome has been reported, causal relationship has not been established.

Heart failure occurred uncommonly during double-blind clinical studies of rosiglitazone in combination with SU (0.6%) or metformin (0.3%) but was reported with a four-fold higher incidence during studies of rosiglitazone in combination with insulin (2.5%).
In 24 month studies, rosiglitazone treatment was associated with a mean increase of 3.7% in weight in combination with metformin and a mean increase of 6.3% in combination with SU.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihyperglycaemic, ATC code: A10 BG 02

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

Preclinical data

The antihyperglycaemic activity of rosiglitazone has been demonstrated in a number of animal models of type 2 diabetes. In addition, rosiglitazone preserved β-cell function as shown by increased pancreatic islet mass and insulin content and prevented the development of overt hyperglycaemia in animal models of type 2 diabetes. Rosiglitazone did not stimulate pancreatic insulin secretion or induce hypoglycaemia in rats and mice. The major metabolite (para-hydroxy-sulphate) with high affinity to the soluble human PPARγ, exhibited relatively high potency in a glucose tolerance assay in obese mouse. The clinical relevance of this observation has not been fully elucidated.
Clinical trials data

The glucose lowering effects observed with rosiglitazone are gradual in onset with near maximal reductions in fasting plasma glucose (FPG) evident following approximately 8 weeks of therapy. Rosiglitazone was associated with increases in weight.

Consistent with the mechanism of action of rosiglitazone, results from a homeostatic model assessment (HOMA) indicate reduced insulin resistance and improved pancreatic β-cell function with rosiglitazone in combination with sulphonylurea or metformin. Improved glycaemic control was also associated with significant decreases in free fatty acids. As a consequence of different but complementary mechanisms of action, combination therapy of rosiglitazone with a sulphonylurea or metformin resulted in additive effects on glycaemic control in type 2 diabetic patients.

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

The efficacy of rosiglitazone in combination with SU or metformin has not been compared to the combination of SU plus metformin. There are no studies assessing long-term cardiovascular outcome in patients receiving rosiglitazone in combination with a sulphonylurea or metformin.

5.2 Pharmacokinetic properties

Absorption:

Absolute bioavailability of rosiglitazone following both a 4 and an 8 mg oral dose is approximately 99%. Rosiglitazone plasma concentrations peak at around 1 hour after dosing. Plasma concentrations are approximately dose proportional over the therapeutic dose range.

Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), although a small decrease in C_max (approx 20-28%) and a delay in t_max (ca.1.75 h) were observed compared to dosing in the fasting state. These small changes are not clinically significant and, therefore, it is not necessary to administer rosiglitazone at any particular time in relation to meals. The absorption of rosiglitazone is not affected by increases in gastric pH.

Distribution:
The volume of distribution of rosiglitazone is approximately 14 litres in healthy volunteers. Plasma protein binding of rosiglitazone is high (approximately 99.8%) and is not influenced by concentration or age. The protein binding of the major metabolite (para-hydroxy-sulphate) is very high (>99.9%).

Metabolism:

Metabolism of rosiglitazone is extensive with no parent compound being excreted unchanged. The major routes of metabolism are N-demethylation and hydroxylation, followed by conjugation with sulphate and glucuronic acid. The contribution of the major metabolite (para-hydroxy-sulphate) to the overall anti-diabetic activity of rosiglitazone has not been fully elucidated in man and it cannot be ruled out that the metabolite may contribute to the activity. However, this raises no safety concern regarding target or special populations as hepatic impairment is contraindicated and the phase III clinical studies included a considerable number of elderly patients and patients with mild to moderate renal impairment.

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

Since there is no significant in vitro inhibition of CYP1A2, 2A6, 2C19, 2D6, 2E1, 3A or 4A with rosiglitazone, there is a low probability of significant metabolism-based interactions with substances metabolised by these P450 enzymes. Rosiglitazone showed moderate inhibition of CYP2C8 (IC₅₀ 18 µM) and low inhibition of CYP2C9 (IC₅₀ 50 µM) in vitro (see section 4.5). An in vivo interaction study with warfarin indicated that rosiglitazone does not interact with CYP2C9 substrates in vivo.

Elimination:

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

Special populations:

Gender: In the pooled population pharmacokinetic analysis, there were no marked differences in the pharmacokinetics of rosiglitazone between males and females.
Elderly: In the pooled population pharmacokinetic analysis, age was not found to influence the pharmacokinetics of rosiglitazone to any significant extent.

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

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

5.3 Preclinical safety data

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

**Film coating:**

Opadry pink OY-L-24802 (hypromellose 6cP, titanium dioxide E171, macrogol 3000, lactose monohydrate, glycerol triacetate, iron oxide red E172).

6.2 **Incompatibilities**

Not applicable.

6.3 **Shelf-life**

2 years.

6.4 **Special precautions for storage**

No special precautions for storage.

6.5 **Nature and content of container**


6.6 **Instructions for use and handling, and disposal (if appropriate)**

No special requirements.

7. **MARKETING AUTHORISATION HOLDER**
8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 4 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains rosiglitazone maleate corresponding to 4 mg rosiglitazone.

For excipients see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

Orange film-coated tablets marked "SB" on one side and "4" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rosiglitazone is indicated only in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea:

– in combination with metformin only in obese patients.

– in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated.
4.2 Posology and method of administration

Treatment should only be initiated by a physician experienced in the treatment of type 2 diabetes.

Experience from clinical trials with rosiglitazone is currently limited to 2 years. The long-term benefits of therapy with rosiglitazone have not been demonstrated (see section 5.1).

Rosiglitazone therapy is usually initiated at 4 mg/day.

**Combination with Metformin**

This dose can be increased to 8 mg/day after 8 weeks if greater glycaemic control is required.

**Combination with sulphonylurea**

There is currently no experience with doses of rosiglitazone above 4 mg/day in combination with sulphonylureas.

Rosiglitazone may be given once or twice a day.

Rosiglitazone may be taken with or without food.

**Elderly**

No dose adjustment is required in the elderly.

**Patients with renal impairment**

No dose adjustment is required in patients with mild and moderate renal insufficiency. Rosiglitazone should not be used in patients with severe renal insufficiency.
Patients with hepatic impairment

Rosiglitazone should not be used in patients with hepatic impairment.

Children and adolescents

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

4.3 Contraindications

Use of rosiglitazone is contraindicated in patients with:

– known hypersensitivity to rosiglitazone or to any of the excipients of the tablet, or

– cardiac failure or history of cardiac failure (NYHA stages I to IV), or

– hepatic impairment.

Rosiglitazone is also contraindicated for use in combination with insulin.

4.4 Special warnings and special precautions for use

There is no clinical experience with rosiglitazone in triple combination with other oral anti-diabetic anti-diabetics.

Rosiglitazone should not be used in monotherapy.

Fluid retention and cardiac failure

Rosiglitazone, can cause fluid retention which may exacerbate or precipitate heart failure. Patients should be observed for signs and symptoms of heart failure, particularly those with reduced cardiac reserve. Rosiglitazone should be discontinued if any deterioration in cardiac
status occurs. An increased incidence of cardiac failure has been observed in clinical trials when rosiglitazone is used in combination with insulin. Therefore rosiglitazone is contraindicated in combination with insulin. Heart failure was also reported more frequently in patients with a history of heart failure, in elderly patients and in patients with mild or moderate renal failure. Since NSAIDs and rosiglitazone are associated with fluid retention, concomitant administration may increase the risk of oedema.

**Monitoring of liver function**

There have been rare reports of hepatocellular dysfunction during post-marketing experience (see section 4.8). It is recommended, therefore, that patients treated with rosiglitazone undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with rosiglitazone in all patients. Therapy with rosiglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal) or with any other evidence of liver disease. Following initiation of therapy with rosiglitazone, it is recommended that liver enzymes be monitored every two months for the first twelve months, and periodically thereafter. If ALT levels are increased to >3X upper limit of normal during rosiglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with rosiglitazone should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

**Weight gain**

In clinical trials with rosiglitazone there was evidence of weight gain, therefore weight should be closely monitored.
**Anaemia**

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

**Others**

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

Rosiglitazone has not been studied in patients with severe renal impairment and is therefore not recommended in these patients.

Caution should be used when administering paclitaxel and rosiglitazone concomitantly (see section 4.5).

**4.5 Interaction with other medicinal products and other forms of interaction**

*In vitro* studies demonstrate that rosiglitazone is predominantly metabolised by CYP2C8, with CYP2C9 as only a minor pathway. *No in vivo* interaction studies have been performed with CYP2C8 substrates (e.g. cerivastatin and paclitaxel). The potential for a clinically relevant interaction with cerivastatin is considered to be low. Although rosiglitazone is not anticipated to affect the pharmacokinetics of paclitaxel, concomitant use is likely to result in inhibition of the metabolism of rosiglitazone. Therefore caution should be used during concomitant administration with paclitaxel. Clinically significant interactions with CYP2C9 substrates or inhibitors are not anticipated.

Concomitant administration with the oral anti-diabetic agents metformin, glibenclamide and acarbose did not result in any clinically relevant pharmacokinetic interactions with rosiglitazone. Moderate ingestion of alcohol with rosiglitazone has no effect on glycaemic control.
No clinically relevant interactions with digoxin, the CYP2C9 substrate warfarin, the CYP3A4 substrates nifedipine, ethinylestradiol or norethindrone were observed after co-administration with rosiglitazone.

4.6 Pregnancy and lactation

There are no adequate data of the use of rosiglitazone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Rosiglitazone should not be used during pregnancy.

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

4.7 Effects on ability to drive and use machines

No effects on the ability to drive or operate machinery have been observed.

4.8 Undesirable effects

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

ROSIGLITAZONE IN COMBINATION WITH METFORMIN

Red Blood Cell

Common: anaemia.

Metabolism and Nutritional

Common: hypoglycaemia, hyperglycaemia.
Uncommon: hyperlipaemia, acidosis lactic, diabetes mellitus aggravated, hypercholesterolaemia.

**Central and Peripheral Nervous System**
Common: headache.
Uncommon: dizziness.

**Gastrointestinal System**
Common: diarrhoea, flatulence, nausea, abdominal pain, dyspepsia.
Uncommon: vomiting, anorexia, constipation.

**Body as a Whole General**
Common: fatigue.

**ROSIGLITAZONE IN COMBINATION WITH SULPHONYLUREA**

**Red blood cell**
Uncommon: anaemia.

**Platelet Bleeding and Clotting**
Uncommon: thrombocytopenia.

**Metabolism and Nutritional**
Common: hypoglycaemia, hyperglycaemia, weight increase.
Uncommon: hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia.

**Psychiatric**
Uncommon: somnolence.
Central and Peripheral Nervous System

Uncommon: dizziness, headache, paresthesia.

Respiratory

Uncommon: dyspnea.

Gastrointestinal

Uncommon: abdominal pain, flatulence, nausea, appetite increased.

Skin and appendages

Uncommon: alopecia, rash.

Body as a whole general

Uncommon: fatigue, asthenia.

In double blind studies, oedema occurred in 3.0% of patients treated with rosiglitazone + sulphonylurea and in 4.4% of patients treated with rosiglitazone + metformin. The incidence of anaemia was higher when rosiglitazone was used in combination with metformin. Adverse experiences of hypercholesterolaemia were reported in 3.6% and 2.1% of patients treated with rosiglitazone + sulphonylurea and rosiglitazone + metformin respectively. 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.

In 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 also low (0.6% rosiglitazone + sulphonylurea; 0.5% rosiglitazone + metformin) compared to an incidence of 0.7% for placebo. Isolated cases of elevated liver enzymes and hepatocellular dysfunction have occurred in post-marketing experience. Although in very rare cases fatal outcome has been reported, causal relationship has not been established.

Heart failure occurred uncommonly during double-blind clinical studies of rosiglitazone in combination with SU (0.6%) or metformin (0.3%) but was reported with a four-fold higher incidence during studies of rosiglitazone in combination with insulin (2.5%).
In 24 month studies, rosiglitazone treatment was associated with a mean increase of 3.7% in weight in combination with metformin and a mean increase of 6.3% in combination with SU.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihyperglycaemic, ATC code: A10 BG 02

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

Preclinical data

The antihyperglycaemic activity of rosiglitazone has been demonstrated in a number of animal models of type 2 diabetes. In addition, rosiglitazone preserved β-cell function as shown by increased pancreatic islet mass and insulin content and prevented the development of overt hyperglycaemia in animal models of type 2 diabetes. Rosiglitazone did not stimulate pancreatic insulin secretion or induce hypoglycaemia in rats and mice. The major metabolite (para-hydroxy-sulphate) with high affinity to the soluble human PPARγ, exhibited relatively high potency in a glucose tolerance assay in obese mouse. The clinical relevance of this observation has not been fully elucidated.
Clinical trials data

The glucose lowering effects observed with rosiglitazone are gradual in onset with near maximal reductions in fasting plasma glucose (FPG) evident following approximately 8 weeks of therapy. Rosiglitazone was associated with increases in weight.

Consistent with the mechanism of action of rosiglitazone, results from a homeostatic model assessment (HOMA) indicate reduced insulin resistance and improved pancreatic β-cell function with rosiglitazone in combination with sulphonylurea or metformin. Improved glycaemic control was also associated with significant decreases in free fatty acids. As a consequence of different but complementary mechanisms of action, combination therapy of rosiglitazone with a sulphonylurea or metformin resulted in additive effects on glycaemic control in type 2 diabetic patients.

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

The efficacy of rosiglitazone in combination with SU or metformin has not been compared to the combination of SU plus metformin. There are no studies assessing long-term cardiovascular outcome in patients receiving rosiglitazone in combination with a sulphonylurea or metformin.

5.2 Pharmacokinetic properties

Absorption:

Absolute bioavailability of rosiglitazone following both a 4 and an 8 mg oral dose is approximately 99%. Rosiglitazone plasma concentrations peak at around 1 hour after dosing. Plasma concentrations are approximately dose proportional over the therapeutic dose range.

Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), although a small decrease in $C_{\text{max}}$ (approx 20-28%) and a delay in $t_{\text{max}}$ (ca.1.75 h) were observed compared to dosing in the fasting state. These small changes are not clinically significant and, therefore, it is not necessary to administer rosiglitazone at any particular time in relation to meals. The absorption of rosiglitazone is not affected by increases in gastric pH.

Distribution:
The volume of distribution of rosiglitazone is approximately 14 litres in healthy volunteers. Plasma protein binding of rosiglitazone is high (approximately 99.8%) and is not influenced by concentration or age. The protein binding of the major metabolite (para-hydroxy-sulphate) is very high (>99.9%).

**Metabolism:**

Metabolism of rosiglitazone is extensive with no parent compound being excreted unchanged. The major routes of metabolism are N-demethylation and hydroxylation, followed by conjugation with sulphate and glucuronic acid. The contribution of the major metabolite (para-hydroxy-sulphate) to the overall anti-diabetic activity of rosiglitazone has not been fully elucidated in man and it cannot be ruled out that the metabolite may contribute to the activity. However, this raises no safety concern regarding target or special populations as hepatic impairment is contraindicated and the phase III clinical studies included a considerable number of elderly patients and patients with mild to moderate renal impairment.

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

Since there is no significant *in vitro* inhibition of CYP1A2, 2A6, 2C19, 2D6, 2E1, 3A or 4A with rosiglitazone, there is a low probability of significant metabolism-based interactions with substances metabolised by these P450 enzymes. Rosiglitazone showed moderate inhibition of CYP2C8 (IC₅₀ 18 µM) and low inhibition of CYP2C9 (IC₅₀ 50 µM) *in vitro* (see section 4.5). An *in vivo* interaction study with warfarin indicated that rosiglitazone does not interact with CYP2C9 substrates *in vivo*.

**Elimination:**

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

**Special populations:**

Gender: In the pooled population pharmacokinetic analysis, there were no marked differences in the pharmacokinetics of rosiglitazone between males and females.
Elderly: In the pooled population pharmacokinetic analysis, age was not found to influence the pharmacokinetics of rosiglitazone to any significant extent.

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

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

5.3 Preclinical safety data

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

**Film coating:**

Opadry orange OY-L-23028 (hypromellose 6cP, titanium dioxide E171, macrogol 3000, purified talc, lactose monohydrate, glycerol triacetate, iron oxide red E172, iron oxide yellow E172).

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf-life**

2 years.

**6.4 Special precautions for storage**

No special precautions for storage.

**6.5 Nature and content of container**


**6.6 Instructions for use and handling, and disposal (if appropriate)**

No special requirements.
7. MARKETING AUTHORISATION HOLDER

SmithKline Beecham plc, New Horizons Court, Brentford, Middlesex, TW8 9EP, United Kingdom.

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

AVANDIA 8 mg film-coated tablets.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains rosiglitazone maleate corresponding to 8 mg rosiglitazone.

For excipients see 6.1.

3. **PHARMACEUTICAL FORM**

Film-coated tablets

Red-brown film-coated tablets marked "SB" on one side and "8" on the other.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Rosiglitazone is indicated only in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea:

- in combination with metformin only in obese patients.
- in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated.
4.2 Posology and method of administration

Treatment should only be initiated by a physician experienced in the treatment of type 2 diabetes.

Experience from clinical trials with rosiglitazone is currently limited to 2 years. The long-term benefits of therapy with rosiglitazone have not been demonstrated (see section 5.1).

Rosiglitazone therapy is usually initiated at 4 mg/day.

Combination with Metformin

This dose can be increased to 8 mg/day after 8 weeks if greater glycaemic control is required.

Combination with sulphonylurea

There is currently no experience with doses of rosiglitazone above 4 mg/day in combination with sulphonylureas.

Rosiglitazone may be given once or twice a day.

Rosiglitazone may be taken with or without food.

Elderly

No dose adjustment is required in the elderly.

Patients with renal impairment

No dose adjustment is required in patients with mild and moderate renal insufficiency. Rosiglitazone should not be used in patients with severe renal insufficiency.
Patients with hepatic impairment

Rosiglitazone should not be used in patients with hepatic impairment.

Children and adolescents

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

4.3 Contraindications

Use of rosiglitazone is contraindicated in patients with:

- known hypersensitivity to rosiglitazone or to any of the excipients of the tablet, or

- cardiac failure or history of cardiac failure (NYHA stages I to IV), or

- hepatic impairment.

Rosiglitazone is also contraindicated for use in combination with insulin.

4.4 Special warnings and special precautions for use

There is no clinical experience with rosiglitazone in triple combination with other oral antidiabetics.

Rosiglitazone should not be used in monotherapy.

Fluid retention and cardiac failure

Rosiglitazone, can cause fluid retention which may exacerbate or precipitate heart failure. Patients should be observed for signs and symptoms of heart failure, particularly those with reduced cardiac reserve. Rosiglitazone should be discontinued if any deterioration in cardiac
status occurs. An increased incidence of cardiac failure has been observed in clinical trials when rosiglitazone is used in combination with insulin. Therefore rosiglitazone is contraindicated in combination with insulin. Heart failure was also reported more frequently in patients with a history of heart failure, in elderly patients and in patients with mild or moderate renal failure. Since NSAIDs and rosiglitazone are associated with fluid retention, concomitant administration may increase the risk of oedema.

**Monitoring of liver function**

There have been rare reports of hepatocellular dysfunction during post-marketing experience (see section 4.8). It is recommended, therefore, that patients treated with rosiglitazone undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with rosiglitazone in all patients. Therapy with rosiglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal) or with any other evidence of liver disease. Following initiation of therapy with rosiglitazone, it is recommended that liver enzymes be monitored every two months for the first twelve months, and periodically thereafter. If ALT levels are increased to >3X upper limit of normal during rosiglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with rosiglitazone should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

**Weight gain**

In clinical trials with rosiglitazone there was evidence of weight gain, therefore weight should be closely monitored.
**Anaemia**

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

**Others**

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

Rosiglitazone has not been studied in patients with severe renal impairment and is therefore not recommended in these patients.

Caution should be used when administering paclitaxel and rosiglitazone concomitantly (see section 4.5).

**4.5 Interaction with other medicinal products and other forms of interaction**

*In vitro* studies demonstrate that rosiglitazone is predominantly metabolised by CYP2C8, with CYP2C9 as only a minor pathway. *No in vivo* interaction studies have been performed with CYP2C8 substrates (e.g. cerivastatin and paclitaxel). The potential for a clinically relevant interaction with cerivastatin is considered to be low. Although rosiglitazone is not anticipated to affect the pharmacokinetics of paclitaxel, concomitant use is likely to result in inhibition of the metabolism of rosiglitazone. Therefore caution should be used during concomitant administration with paclitaxel. Clinically significant interactions with CYP2C9 substrates or inhibitors are not anticipated.

Concomitant administration with the oral anti-diabetic agents metformin, glibenclamide and acarbose did not result in any clinically relevant pharmacokinetic interactions with rosiglitazone. Moderate ingestion of alcohol with rosiglitazone has no effect on glycaemic control.
No clinically relevant interactions with digoxin, the CYP2C9 substrate warfarin, the CYP3A4 substrates nifedipine, ethinylestradiol or norethindrone were observed after co-administration with rosiglitazone.

4.6 Pregnancy and lactation

There are no adequate data of the use of rosiglitazone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Rosiglitazone should not be used during pregnancy.

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

4.7 Effects on ability to drive and use machines

No effects on the ability to drive or operate machinery have been observed.

4.8 Undesirable effects

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

**ROSIGLITAZONE IN COMBINATION WITH METFORMIN**

**Red Blood Cell**

Common: anaemia.

**Metabolism and Nutritional**

Common: hypoglycaemia, hyperglycaemia.
Uncommon: hyperlipaemia, acidosis lactic, diabetes mellitus aggravated, hypercholesterolaemia.

Central and Peripheral Nervous System
Common: headache.
Uncommon: dizziness.

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

Body as a Whole General
Common: fatigue.

ROSIGLITAZONE IN COMBINATION WITH SULPHONYLUREA

Red blood cell
Uncommon: anaemia.

Platelet Bleeding and Clotting
Uncommon: thrombocytopenia.

Metabolism and Nutritional
Common: hypoglycaemia, hyperglycaemia, weight increase.
Uncommon: hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia.

Psychiatric
Uncommon: somnolence.
Central and Peripheral Nervous System
Uncommon: dizziness, headache, paresthesia.

Respiratory
Uncommon: dyspnea.

Gastrointestinal
Uncommon: abdominal pain, flatulence, nausea, appetite increased.

Skin and appendages
Uncommon: alopecia, rash.

Body as a whole general
Uncommon: fatigue, asthenia.

In double blind studies, oedema occurred in 3.0% of patients treated with rosiglitazone + sulphonylurea and in 4.4% of patients treated with rosiglitazone + metformin. The incidence of anaemia was higher when rosiglitazone was used in combination with metformin. Adverse experiences of hypercholesterolaemia were reported in 3.6% and 2.1% of patients treated with rosiglitazone + sulphonylurea and rosiglitazone + metformin respectively. 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.

In 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 also low (0.6% rosiglitazone + sulphonylurea; 0.5% rosiglitazone + metformin) compared to an incidence of 0.7% for placebo. Isolated cases of elevated liver enzymes and hepatocellular dysfunction have occurred in post-marketing experience. Although in very rare cases fatal outcome has been reported, causal relationship has not been established.

Heart failure occurred uncommonly during double-blind clinical studies of rosiglitazone in combination with SU (0.6%) or metformin (0.3%) but was reported with a four-fold higher incidence during studies of rosiglitazone in combination with insulin (2.5%).
In 24 month studies, rosiglitazone treatment was associated with a mean increase of 3.7% in weight in combination with metformin and a mean increase of 6.3% in combination with SU.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihyperglycaemic, ATC code: A10 BG 02

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

Preclinical data

The antihyperglycaemic activity of rosiglitazone has been demonstrated in a number of animal models of type 2 diabetes. In addition, rosiglitazone preserved \(\beta\)-cell function as shown by increased pancreatic islet mass and insulin content and prevented the development of overt hyperglycaemia in animal models of type 2 diabetes. Rosiglitazone did not stimulate pancreatic insulin secretion or induce hypoglycaemia in rats and mice. The major metabolite (para-hydroxy-sulphate) with high affinity to the soluble human PPAR\(\gamma\), exhibited relatively high potency in a glucose tolerance assay in obese mouse. The clinical relevance of this observation has not been fully elucidated.
Clinical trials data

The glucose lowering effects observed with rosiglitazone are gradual in onset with near maximal reductions in fasting plasma glucose (FPG) evident following approximately 8 weeks of therapy. Rosiglitazone was associated with increases in weight.

Consistent with the mechanism of action of rosiglitazone, results from a homeostatic model assessment (HOMA) indicate reduced insulin resistance and improved pancreatic β-cell function with rosiglitazone in combination with sulphonylurea or metformin. Improved glycaemic control was also associated with significant decreases in free fatty acids. As a consequence of different but complementary mechanisms of action, combination therapy of rosiglitazone with a sulphonylurea or metformin resulted in additive effects on glycaemic control in type 2 diabetic patients.

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

The efficacy of rosiglitazone in combination with SU or metformin has not been compared to the combination of SU plus metformin. There are no studies assessing long-term cardiovascular outcome in patients receiving rosiglitazone in combination with a sulphonylurea or metformin.

5.2 Pharmacokinetic properties

Absorption:

Absolute bioavailability of rosiglitazone following both a 4 and an 8 mg oral dose is approximately 99%. Rosiglitazone plasma concentrations peak at around 1 hour after dosing. Plasma concentrations are approximately dose proportional over the therapeutic dose range.

Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), although a small decrease in $C_{\text{max}}$ (approx 20-28%) and a delay in $t_{\text{max}}$ (ca. 1.75 h) were observed compared to dosing in the fasting state. These small changes are not clinically significant and, therefore, it is not necessary to administer rosiglitazone at any particular time in relation to meals. The absorption of rosiglitazone is not affected by increases in gastric pH.

Distribution:
The volume of distribution of rosiglitazone is approximately 14 litres in healthy volunteers. Plasma protein binding of rosiglitazone is high (approximately 99.8%) and is not influenced by concentration or age. The protein binding of the major metabolite (para-hydroxy-sulphate) is very high (>99.9%).

**Metabolism:**

Metabolism of rosiglitazone is extensive with no parent compound being excreted unchanged. The major routes of metabolism are N-demethylation and hydroxylation, followed by conjugation with sulphate and glucuronic acid. The contribution of the major metabolite (para-hydroxy-sulphate) to the overall anti-diabetic activity of rosiglitazone has not been fully elucidated in man and it cannot be ruled out that the metabolite may contribute to the activity. However, this raises no safety concern regarding target or special populations as hepatic impairment is contraindicated and the phase III clinical studies included a considerable number of elderly patients and patients with mild to moderate renal impairment.

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

Since there is no significant *in vitro* inhibition of CYP1A2, 2A6, 2C19, 2D6, 2E1, 3A or 4A with rosiglitazone, there is a low probability of significant metabolism-based interactions with substances metabolised by these P450 enzymes. Rosiglitazone showed moderate inhibition of CYP2C8 (IC₅₀ 18 µM) and low inhibition of CYP2C9 (IC₅₀ 50 µM) *in vitro* (see section 4.5). An *in vivo* interaction study with warfarin indicated that rosiglitazone does not interact with CYP2C9 substrates *in vivo*.

**Elimination:**

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

**Special populations:**

Gender: In the pooled population pharmacokinetic analysis, there were no marked differences in the pharmacokinetics of rosiglitazone between males and females.
Elderly: In the pooled population pharmacokinetic analysis, age was not found to influence the pharmacokinetics of rosiglitazone to any significant extent.

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

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

5.3 Preclinical safety data

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Film coating:

Opadry pink OY-L-24803 (hypromellose 6cP, titanium dioxide E171, macrogol 3000, lactose monohydrate, glycerol triacetate, iron oxide red E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and content of container


6.6 Instructions for use and handling, and disposal (if appropriate)

No special requirements.

7. MARKETING AUTHORISATION HOLDER
8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II

A. MANUFACTURING AUTHORITY / 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

SmithKline Beecham Laboratoires Pharmaceutiques, Z.I. Du Terras, 53100 Mayenne, France

Manufacturing Authorisation was issued on 29 May 1996 by the Agence du Medicament

B. CONDITIONS OF THE MARKETING AUTHORISATION

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

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

- OTHER CONDITIONS

For five years after the granting of the Marketing Authorisation, detailed records of all suspected adverse reactions occurring within or outside the Community which are reported to the Marketing Authorisation Holder shall be submitted to the Agency and to the Member States every six months.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 1 mg film-coated tablets
rosiglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rosiglitazone maleate corresponding to 1 mg rosiglitazone

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For oral 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

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

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 plc
New Horizons Court
Brentford, Middlesex TW8 9EP
12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 1 mg tablets
rosiglitazone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham plc

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 2 mg film-coated tablets
rosiglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rosiglitazone maleate corresponding to 2 mg rosiglitazone

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For oral 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

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Use only as directed by your doctor

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 plc
New Horizons Court
Brentford, Middlesex TW8 9EP
United Kingdom

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EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 2 mg film-coated tablets
rosiglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rosiglitazone maleate corresponding to 2 mg rosiglitazone

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

112 film-coated tablets

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For oral 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**

Read the package leaflet before use

Use only as directed by your doctor

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 plc

New Horizons Court

Brentford, Middlesex TW8 9EP

71
United Kingdom

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/00/000/000

13. MANUFACTURER'S BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 2 mg film-coated tablets

rosiglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rosiglitazone maleate corresponding to 2 mg rosiglitazone

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets

unit dose pack

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For oral 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

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

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

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Brentford, Middlesex TW8 9EP
12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/00/000/000

13. MANUFACTURER’S BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 2 mg tablets
rosiglitazone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham plc

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 4 mg film-coated tablets
rosiglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rosiglitazone maleate corresponding to 4 mg rosiglitazone

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For oral 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

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

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

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EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 4 mg film-coated tablets
rosiglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rosiglitazone maleate corresponding to 4 mg rosiglitazone

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For oral 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

Read the package leaflet before use

Use only as directed by your doctor

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

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EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE
1. **NAME OF THE MEDICINAL PRODUCT**

AVANDIA 4 mg film-coated tablets

rosiglitazone

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains rosiglitazone maleate corresponding to 4 mg rosiglitazone

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

56 film-coated tablets

5. **METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION**

For oral 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**

Read the package leaflet before use

Use only as directed by your doctor

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 plc

New Horizons Court

Brentford, Middlesex TW8 9EP
12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 4 mg film-coated tablets
rosiglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rosiglitazone maleate corresponding to 4 mg rosiglitazone

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

112 film-coated tablets

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For oral 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**

Read the package leaflet before use

Use only as directed by your doctor

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**

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Brentford, Middlesex TW8 9EP
12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 4 mg film-coated tablets
rosiglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rosiglitazone maleate corresponding to 4 mg rosiglitazone

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets
unit dose pack

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For oral 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

Read the package leaflet before use

Use only as directed by your doctor

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 plc

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Brentford, Middlesex TW8 9EP
12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 4 mg tablets
rosiglitazone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

SmithKline Beecham plc

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 8 mg film-coated tablets
rosiglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rosiglitazone maleate corresponding to 8 mg rosiglitazone

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For oral 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

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

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 plc
New Horizons Court
Brentford, Middlesex TW8 9EP
12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 8 mg film-coated tablets
rosiglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rosiglitazone maleate corresponding to 8 mg rosiglitazone

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For oral 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

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

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 plc
New Horizons Court
Brentford, Middlesex TW8 9EP
12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

AVANDIA 8 mg film-coated tablets
rosiglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rosiglitazone maleate corresponding to 8 mg rosiglitazone

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

112 film-coated tablets

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For oral 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

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

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 plc
New Horizons Court
Brentford, Middlesex TW8 9EP
12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. **NAME OF THE MEDICINAL PRODUCT**

   AVANDIA 8 mg tablets
   rosiglitazone

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

   SmithKline Beecham plc

3. **EXPIRY DATE**

   EXP

4. **BATCH NUMBER**

   LOT
B. PACKAGE LEAFLET
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 further questions, please ask your doctor or your pharmacist.
− This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What AVANDIA is and what it is used for
2. Before you take AVANDIA
3. How to take AVANDIA
4. Possible side effects
5. Storing AVANDIA

[Name of the medicinal product]

AVANDIA 1 mg film-coated tablets
rosiglitazone

[Full statement of the active substance(s) and excipient(s)]

The active substance is rosiglitazone. Each tablet contains rosiglitazone maleate corresponding to 1 mg rosiglitazone.

The other ingredients are:

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

Film coating:

Opadry yellow OY-L-22809 (hypromellose 6cP, titanium dioxide E171, macrogol 3000, lactose monohydrate, glycerol triacetate, iron oxide yellow E172).

[Name and address of the marketing authorisation holder and of the manufacturing authorisation holder responsible for batch release, if different]

Marketing Authorisation Holder: SmithKline Beecham plc, New Horizons Court, Brentford, Middlesex TW8 9EP, United Kingdom.

Manufacturer: SmithKline Beecham Laboratoires Pharmaceutiques, Z1 du Terras, 53100 Mayenne, France.

1. WHAT AVANDIA IS AND WHAT IT IS USED FOR

[Pharmaceutical form and contents; pharmacotherapeutic group]

AVANDIA is supplied to you as yellow, film-coated tablets. They are marked "SB" on one side and "1" on the other.

The tablets are provided in blister packs containing 56 film-coated tablets.

[Therapeutic indications]

AVANDIA is an anti-diabetic medicine taken by mouth to treat Type 2 (non-insulin dependent) diabetes mellitus.

Type 2 diabetes mellitus is a condition in which your body does not make enough insulin or where the insulin that your body produces does not work as well as it should. Insulin is a natural body chemical that helps you control your blood sugar levels. By helping your body make better use of the insulin it produces AVANDIA helps to reduce your blood sugar towards a normal level.
AVANDIA should be used only with metformin or a sulphonylurea which are also oral anti-diabetic medicines.

2. BEFORE YOU TAKE AVANDIA

[List of information necessary before taking the medicinal product]

[Contraindications]

Do not take AVANDIA:

– If you are hypersensitive (allergic) to rosiglitazone or any of the other ingredients of AVANDIA.
– If you have a heart condition.
– If you have a liver disease.
– If you already take insulin.

[Appropriate precautions for use: special warnings]

Take special care with AVANDIA:

Tell your doctor before you start to take this medicine:

– If you are planning to become pregnant.
– If you are breastfeeding.
– If you have polycystic ovary syndrome. Due to the way your medicine works there may be an increased likelihood of your becoming pregnant.
– If you have a problem with your liver, heart or kidneys.
– If you already take a sulphonylurea and metformin, since triple combination is not recommended.
– There is no information available on the use of AVANDIA in people under 18 years of age, therefore its use in these patients is not recommended.

[Interactions with food and drink]

Taking AVANDIA with food and drink:
Your tablets may be taken with or after a meal or on an empty stomach. Swallow the tablets with a glass of water.

[Use by pregnant or breast-feeding women]

Pregnancy:
Tell your doctor if you are, you think you might be or are planning to become pregnant. Your doctor will advise you to discontinue this medicine.

Breast-feeding:
Tell your doctor if you are breast-feeding or if you are planning to breast-feed your baby. Your doctor will discontinue this medicine.

[Effects on the ability to drive or to use machines]

Driving and using machines:
This medicine will not affect your ability to drive or operate machinery.

Important information about some of the ingredients of AVANDIA:
Patients who are intolerant to lactose should note that each AVANDIA tablet contains a small amount of lactose (about 111 mg).

[Interaction with other medicinal products]

Taking other medicines:
You can generally continue to take other medicines while you are being treated with AVANDIA. However, always tell your doctor or pharmacist which medicines you are taking, including those you have bought yourself.

3. HOW TO TAKE AVANDIA

[Instructions for proper use]

[Dosage]
Follow your doctor's instructions about how and when to take your tablets otherwise you will not fully benefit from your medicine.

The amount of AVANDIA people take can be different, and this depends on your condition. Your doctor will prescribe the best dose for you.

The usual starting dose of AVANDIA is 4 mg (4 of these tablets) per day, taken as a single dose or as two doses to be taken during the day (e.g. 2 of these tablets in the morning and 2 of these tablets in the evening).

If necessary, your doctor may increase this dose up to 8 mg (8 of these tablets) per day, taken as a single dose or as two doses to be taken during the day (e.g. 4 of these tablets in the morning and 4 of these tablets in the evening).

Your tablets should be swallowed with a glass of water. They may be taken with or after a meal or on an empty stomach. It is best to take the tablets at the same time every day.

If you feel the effect of your medicine is too weak or too strong do not change the dose yourself, but ask your doctor.

Do not take more tablets than your doctor has recommended.

Your doctor will prescribe AVANDIA in combination with other oral anti-diabetic medicines.

Every two months during the first year of taking AVANDIA and thereafter at regular intervals your doctor will ask you to have blood tests to check that your liver is working normally.
If you are following a diabetic weight control diet, you should continue with this while you are taking AVANDIA.

Your weight should be checked at regular intervals; if your weight increases, inform your doctor.

**[Symptoms in case of overdose and actions to be taken]**

**If you take more AVANDIA than you should:**

If you take more AVANDIA than you should or if someone else has taken your medicine, tell a doctor or pharmacist immediately. Show them the package.

**[Actions to be taken when one or more doses have been missed]**

**If you forget to take AVANDIA:**

Take your tablet as soon as you remember. Take your next dose at the usual time. Do not take a double dose to make up for forgotten individual doses.

**4. POSSIBLE SIDE EFFECTS**

**[Description of side effects]**

Like all medicines, AVANDIA can have side effects.

Some patients have experienced the following side effects whilst taking AVANDIA:

- localised swelling (oedema).
- a small reduction in red blood cell count (anaemia).
- weight gain.
- in rare cases your liver function may be impaired.

AVANDIA may increase your total cholesterol level slightly. If you have any concerns about your cholesterol levels, you should speak to your doctor.
If you develop any unusual discomfort, tell your doctor as soon as possible.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. **STORING AVANDIA**

*Storage conditions and expiry date*

Keep out of the reach and sight of children.

Store in the original package.

If your doctor stops your medicine, do not keep any leftover tablets unless your doctor tells you to. Return any unused tablets to your pharmacist who will discard them safely.

Do not use after the expiry date stated on the pack.

This leaflet was last approved in
Further information

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

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Rue du Tilleul 13
B-1332 Genval
Tél/Tel: + 32 2656 2111

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Italia
SmithKline Beecham S.p.A
Via Zambeletti
I-20021 Baranzate di Bollate (Mi)
Tel: +3902 38061
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 further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What AVANDIA is and what it is used for
2. Before you take AVANDIA
3. How to take AVANDIA
4. Possible side effects
5. Storing AVANDIA

[Name of the medicinal product]

AVANDIA 2 mg film-coated tablets

rosiglitazone

[Full statement of the active substance(s) and excipient(s)]

The active substance is rosiglitazone. Each tablet contains rosiglitazone maleate corresponding to 2 mg rosiglitazone.

The other ingredients are:

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

Film coating:

Opadry pink OY-L-24802 (hypromellose 6cP, titanium dioxide E171, macrogol 3000, lactose monohydrate, glycerol triacetate, iron oxide red E172).

**1. WHAT AVANDIA IS AND WHAT IT IS USED FOR**

**[Pharmaceutical form and contents; pharmacotherapeutic group]**

AVANDIA is supplied to you as pink, film-coated tablets. They are marked "SB" on one side and "2" on the other.

The tablets are provided in blister packs containing 56, 112, film-coated tablets or 56 film-coated tablets, unit dose pack.

**[Therapeutic indications]**

AVANDIA is an anti-diabetic medicine taken by mouth to treat Type 2 (non-insulin dependent) diabetes mellitus.

Type 2 diabetes mellitus is a condition in which your body does not make enough insulin or where the insulin that your body produces does not work as well as it should. Insulin is a natural body chemical that helps you control your blood sugar levels. By helping your body make better use of the insulin it produces AVANDIA helps to reduce your blood sugar towards a normal level.
AVANDIA should be used only with metformin or a sulphonylurea which are also oral anti-diabetic medicines.

2. BEFORE YOU TAKE AVANDIA

[List of information necessary before taking the medicinal product]

[Contraindications]

Do not take AVANDIA:

– If you are hypersensitive (allergic) to rosiglitazone or any of the other ingredients of AVANDIA.
– If you have a heart condition.
– If you have a liver disease.
– If you already take insulin.

[Appropriate precautions for use; special warnings]

Take special care with AVANDIA:

Tell your doctor before you start to take this medicine:

– If you are planning to become pregnant.
– If you are breastfeeding.
– If you have polycystic ovary syndrome. Due to the way your medicine works there may be an increased likelihood of your becoming pregnant.
– If you have a problem with your liver, heart or kidneys.
– If you already take a sulphonylurea and metformin, since triple combination is not recommended.
– There is no information available on the use of AVANDIA in people under 18 years of age, therefore its use in these patients is not recommended.

[Interactions with food and drink]

Taking AVANDIA with food and drink:
Your tablets may be taken with or after a meal or on an empty stomach. Swallow the tablets with a glass of water.

**[Use by pregnant or breast-feeding women]**

**Pregnancy:**

Tell your doctor if you are, you think you might be or are planning to become pregnant. Your doctor will advise you to discontinue this medicine.

**Breast-feeding:**

Tell your doctor if you are breast-feeding or if you are planning to breast-feed your baby. Your doctor will discontinue this medicine.

**[Effects on the ability to drive or to use machines]**

**Driving and using machines:**

This medicine will not affect your ability to drive or operate machinery.

**Important information about some of the ingredients of AVANDIA:**

Patients who are intolerant to lactose should note that each AVANDIA tablet contains a small amount of lactose (about 109 mg).

**[Interaction with other medicinal products]**

**Taking other medicines:**

You can generally continue to take other medicines while you are being treated with AVANDIA. However, always tell your doctor or pharmacist which medicines you are taking, including those you have bought yourself.

3. **HOW TO TAKE AVANDIA**

**[Instructions for proper use]**

**[Dosage]**
Follow your doctor's instructions about how and when to take your tablets otherwise you will not fully benefit from your medicine.

The amount of AVANDIA people take can be different, and this depends on your condition. Your doctor will prescribe the best dose for you.

The usual starting dose of AVANDIA is 4 mg (2 of these tablets) per day, taken as a single dose or as two doses to be taken during the day (e.g. 1 of these tablets in the morning and 1 of these tablets in the evening).

If necessary, your doctor may increase this dose up to 8 mg (4 of these tablets) per day, taken as a single dose or as two doses to be taken during the day (e.g. 2 of these tablets in the morning and 2 of these tablets in the evening).

Your tablets should be swallowed with a glass of water. They may be taken with or after a meal or on an empty stomach. It is best to take the tablets at the same time every day.

If you feel the effect of your medicine is too weak or too strong do not change the dose yourself, but ask your doctor.

Do not take more tablets than your doctor has recommended.

Your doctor will prescribe AVANDIA in combination with other oral anti-diabetic medicines.

Every two months during the first year of taking AVANDIA and thereafter at regular intervals your doctor will ask you to have blood tests to check that your liver is working normally.
If you are following a diabetic weight control diet, you should continue with this while you are taking AVANDIA.

Your weight should be checked at regular intervals; if your weight increases, inform your doctor.

**[Symptoms in case of overdose and actions to be taken]**

If you take more AVANDIA than you should:

If you take more AVANDIA than you should or if someone else has taken your medicine, tell a doctor or pharmacist immediately. Show them the package.

**[Actions to be taken when one or more doses have been missed]**

If you forget to take AVANDIA:

Take your tablet as soon as you remember. Take your next dose at the usual time. Do not take a double dose to make up for forgotten individual doses.

4. **POSSIBLE SIDE EFFECTS**

**[Description of side effects]**

Like all medicines, AVANDIA can have side effects.

Some patients have experienced the following side effects whilst taking AVANDIA:

- localised swelling (oedema).
- a small reduction in red blood cell count (anaemia).
- weight gain.
- in rare cases your liver function may be impaired.

AVANDIA may increase your total cholesterol level slightly. If you have any concerns about your cholesterol levels, you should speak to your doctor.
If you develop any unusual discomfort, tell your doctor as soon as possible.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING AVANDIA

[Storage conditions and expiry date]

Keep out of the reach and sight of children.

Store in the original package.

If your doctor stops your medicine, do not keep any leftover tablets unless your doctor tells you to. Return any unused tablets to your pharmacist who will discard them safely.

Do not use after the expiry date stated on the pack.

This leaflet was last approved in
### Further information

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Local Representative</th>
<th>Address</th>
<th>Telephone</th>
</tr>
</thead>
<tbody>
<tr>
<td>België/Belgique/Belgien</td>
<td>SmithKline Beecham SA</td>
<td>Rue du Tilleul B-1332 Genval</td>
<td>+ 32 2656 2111</td>
</tr>
<tr>
<td>Luxembourg/Luxemburg</td>
<td>SmithKline Beecham SA</td>
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</tr>
<tr>
<td>Danmark</td>
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<tr>
<td>Nederland</td>
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<tr>
<td>Ελλάδα</td>
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<td>+ 301 989 0111</td>
</tr>
<tr>
<td>España</td>
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<td>Valle de la Fuenfria 3 E-28034 Madrid</td>
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<tr>
<td>Suomi/Finland</td>
<td>SmithKline Beecham Pharmaceuticals</td>
<td>Metsäneidonkuja 10 FIN-02130 Espoo/Esbo</td>
<td></td>
</tr>
</tbody>
</table>
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I-20021 Baranzate di Bollate (Mi)
Tel: + 3902 38061
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 further questions, please ask your doctor or your pharmacist.
− This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What AVANDIA is and what it is used for
2. Before you take AVANDIA
3. How to take AVANDIA
4. Possible side effects
5. Storing AVANDIA

[Name of the medicinal product]

AVANDIA 4 mg film-coated tablets
rosiglitazone

[Full statement of the active substance(s) and excipient(s)]

The active substance is rosiglitazone. Each tablet contains rosiglitazone maleate corresponding to 4 mg rosiglitazone.

The other ingredients are:

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

Film coating:
Opadry orange OY-L-23028 (hypromellose 6cP, titanium dioxide E171, macrogol 3000, purified talc, lactose monohydrate, glycerol triacetate, iron oxide red E172, iron oxide yellow E172).

[Name and address of the marketing authorisation holder and of the manufacturing authorisation holder responsible for batch release, if different]
Marketing Authorisation Holder: SmithKline Beecham plc, New Horizons Court, Brentford, Middlesex TW8 9EP, United Kingdom.

Manufacturer: SmithKline Beecham Laboratoires Pharmaceutiques, Z1 du Terras, 53100 Mayenne, France.

1. WHAT AVANDIA IS AND WHAT IT IS USED FOR

[Pharmaceutical form and contents; pharmacotherapeutic group]
AVANDIA is supplied to you as orange, film-coated tablets. They are marked "SB" on one side and "4" on the other.

The tablets are provided in blister packs containing 7, 28, 56, 112, film-coated tablets or 56 film-coated tablets, unit dose pack.

[Therapeutic indications]
AVANDIA is an anti-diabetic medicine taken by mouth to treat Type 2 (non-insulin dependent) diabetes mellitus.

Type 2 diabetes mellitus is a condition in which your body does not make enough insulin or where the insulin that your body produces does not work as well as it should. Insulin is a natural body chemical that helps you control your blood sugar levels. By helping your body make better use of the insulin it produces AVANDIA helps to reduce your blood sugar towards a normal level.
AVANDIA should be used only with metformin or a sulphonylurea which are also oral anti-diabetic medicines.

2. BEFORE YOU TAKE AVANDIA

[Contraindications]

Do not take AVANDIA:

− If you are hypersensitive (allergic) to rosiglitazone or any of the other ingredients of AVANDIA.
− If you have a heart condition.
− If you have a liver disease.
− If you already take insulin.

[Appropriate precautions for use; special warnings]

Take special care with AVANDIA:

Tell your doctor before you start to take this medicine:

− If you are planning to become pregnant.
− If you are breastfeeding.
− If you have polycystic ovary syndrome. Due to the way your medicine works there may be an increased likelihood of your becoming pregnant.
− If you have a problem with your liver, heart or kidneys.
− If you already take a sulphonylurea and metformin, since triple combination is not recommended.
− There is no information available on the use of AVANDIA in people under 18 years of age, therefore its use in these patients is not recommended.

[Interactions with food and drink]
Taking AVANDIA with food and drink:

Your tablets may be taken with or after a meal or on an empty stomach. Swallow the tablets with a glass of water.

[Use by pregnant or breast-feeding women]

Pregnancy:

Tell your doctor if you are, you think you might be or are planning to become pregnant. Your doctor will advise you to discontinue this medicine.

Breast-feeding:

Tell your doctor if you are breast-feeding or if you are planning to breast-feed your baby. Your doctor will discontinue this medicine.

[Effects on the ability to drive or to use machines]

Driving and using machines:

This medicine will not affect your ability to drive or operate machinery.

Important information about some of the ingredients of AVANDIA:

Patients who are intolerant to lactose should note that each AVANDIA tablet contains a small amount of lactose (about 105 mg).

[Interaction with other medicinal products]

Taking other medicines:

You can generally continue to take other medicines while you are being treated with AVANDIA. However, always tell your doctor or pharmacist which medicines you are taking, including those you have bought yourself.

3. HOW TO TAKE AVANDIA

[Instructions for proper use]
Follow your doctor’s instructions about how and when to take your tablets otherwise you will not fully benefit from your medicine.

The amount of AVANDIA people take can be different, and this depends on your condition. Your doctor will prescribe the best dose for you.

The usual starting dose of AVANDIA is 4 mg (1 of these tablets) per day. This should be taken as a single dose.

If necessary, your doctor may increase this dose up to 8 mg (2 of these tablets) per day, taken as a single dose or as two doses to be taken during the day (e.g. 1 of these tablets in the morning and 1 of these tablets in the evening).

Your tablets should be swallowed with a glass of water. They may be taken with or after a meal or on an empty stomach. It is best to take the tablets at the same time every day.

If you feel the effect of your medicine is too weak or too strong do not change the dose yourself, but ask your doctor.

Do not take more tablets than your doctor has recommended.

Your doctor will prescribe AVANDIA in combination with other oral anti-diabetic medicines.

Every two months during the first year of taking AVANDIA and thereafter at regular intervals your doctor will ask you to have blood tests to check that your liver is working normally.
If you are following a diabetic weight control diet, you should continue with this while you are taking AVANDIA.

Your weight should be checked at regular intervals; if your weight increases, inform your doctor.

[Symptoms in case of overdose and actions to be taken]

If you take more AVANDIA than you should:

If you take more AVANDIA than you should or if someone else has taken your medicine, tell a doctor or pharmacist immediately. Show them the package.

[Actions to be taken when one or more doses have been missed]

If you forget to take AVANDIA:

Take your tablet as soon as you remember. Take your next dose at the usual time. Do not take a double dose to make up for forgotten individual doses.

4. POSSIBLE SIDE EFFECTS

[Description of side effects]

Like all medicines, AVANDIA can have side effects.

Some patients have experienced the following side effects whilst taking AVANDIA:

– localised swelling (oedema).
– a small reduction in red blood cell count (anaemia).
– weight gain.
– in rare cases your liver function may be impaired.

AVANDIA may increase your total cholesterol level slightly. If you have any concerns about your cholesterol levels, you should speak to your doctor.
If you develop any unusual discomfort, tell your doctor as soon as possible.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. **STORING AVANDIA**

[Storage conditions and expiry date]

Keep out of the reach and sight of children.

Store in the original package.

If your doctor stops your medicine, do not keep any leftover tablets unless your doctor tells you to. Return any unused tablets to your pharmacist who will discard them safely.

Do not use after the expiry date stated on the pack.

**This leaflet was last approved in**
Further information

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

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<th>Country</th>
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<tbody>
<tr>
<td>België/Belgique/Belgien</td>
<td>SmithKline Beecham SA Rue du Tilleul 13 B-1332 Genval</td>
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Via Zambeletti
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Tel: + 3902 38061
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 further questions, please ask your doctor or your pharmacist.
− This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What AVANDIA is and what it is used for
2. Before you take AVANDIA
3. How to take AVANDIA
4. Possible side effects
5. Storing AVANDIA

[Name of the medicinal product]
AVANDIA 8 mg film-coated tablets
rosiglitazone

[Full statement of the active substance(s) and excipient(s)]
The active substance is rosiglitazone. Each tablet contains rosiglitazone maleate corresponding to 8 mg rosiglitazone.

The other ingredients are:

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

Film coating:
Opadry pink OY-L-24803 (hypromellose 6cP, titanium dioxide E171, macrogol 3000, lactose monohydrate, glycerol triacetate, iron oxide red E172).

[Name and address of the marketing authorisation holder and of the manufacturing authorisation holder responsible for batch release, if different]
Marketing Authorisation Holder: SmithKline Beecham plc, New Horizons Court, Brentford, Middlesex TW8 9EP, United Kingdom.

Manufacturer: SmithKline Beecham Laboratoires Pharmaceutiques, Z1 du Terras, 53100 Mayenne, France.

1. WHAT AVANDIA IS AND WHAT IT IS USED FOR

AVANDIA is supplied to you as red-brown, film-coated tablets. They are marked "SB" on one side and "8" on the other.

The tablets are provided in blister packs containing 7, 28, or 112 film-coated tablets.

AVANDIA is an anti-diabetic medicine taken by mouth to treat Type 2 (non-insulin dependent) diabetes mellitus.

Type 2 diabetes mellitus is a condition in which your body does not make enough insulin or where the insulin that your body produces does not work as well as it should. Insulin is a natural body chemical that helps you control your blood sugar levels. By helping your body make better use of the insulin it produces AVANDIA helps to reduce your blood sugar towards a normal level.
AVANDIA should be used only with metformin or a sulphonylurea which are also oral anti-diabetic medicines.

2. BEFORE YOU TAKE AVANDIA

[List of information necessary before taking the medicinal product]

[Contraindications]

Do not take AVANDIA:

– If you are hypersensitive (allergic) to rosiglitazone or any of the other ingredients of AVANDIA.
– If you have a heart condition.
– If you have a liver disease.
– If you already take insulin.

[Appropriate precautions for use: special warnings]

Take special care with AVANDIA:

Tell your doctor before you start to take this medicine:

– If you are planning to become pregnant.
– If you are breastfeeding.
– If you have polycystic ovary syndrome. Due to the way your medicine works there may be an increased likelihood of your becoming pregnant.
– If you have a problem with your liver, heart or kidneys.
– If you already take a sulphonylurea and metformin, since triple combination is not recommended.
– There is no information available on the use of AVANDIA in people under 18 years of age, therefore its use in these patients is not recommended.

[Interactions with food and drink]

Taking AVANDIA with food and drink:
Your tablets may be taken with or after a meal or on an empty stomach. Swallow the tablets with a glass of water.

**[Use by pregnant or breast-feeding women]**

**Pregnancy:**
Tell your doctor if you are, you think you might be or are planning to become pregnant. Your doctor will advise you to discontinue this medicine.

**Breast-feeding:**
Tell your doctor if you are breast-feeding or if you are planning to breast-feed your baby. Your doctor will discontinue this medicine.

**[Effects on the ability to drive or to use machines]**

**Driving and using machines:**
This medicine will not affect your ability to drive or operate machinery.

**Important information about some of the ingredients of AVANDIA:**
Patients who are intolerant to lactose should note that each AVANDIA tablet contains a small amount of lactose (about 210 mg).

**[Interaction with other medicinal products]**

**Taking other medicines:**
You can generally continue to take other medicines while you are being treated with AVANDIA. However, always tell your doctor or pharmacist which medicines you are taking, including those you have bought yourself.

3. **HOW TO TAKE AVANDIA**

**[Instructions for proper use]**

**[Dosage]**
Follow your doctor's instructions about how and when to take your tablets otherwise you will not fully benefit from your medicine.

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**[Symptoms in case of overdose and actions to be taken]**

**If you take more AVANDIA than you should:**

If you take more AVANDIA than you should or if someone else has taken your medicine, tell a doctor or pharmacist immediately. Show them the package.

**[Actions to be taken when one or more doses have been missed]**

**If you forget to take AVANDIA:**

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4. **POSSIBLE SIDE EFFECTS**

**[Description of side effects]**

Like all medicines, AVANDIA can have side effects.

Some patients have experienced the following side effects whilst taking AVANDIA:

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- weight gain.
- in rare cases your liver function may be impaired.

AVANDIA may increase your total cholesterol level slightly. If you have any concerns about your cholesterol levels, you should speak to your doctor.
If you develop any unusual discomfort, tell your doctor as soon as possible.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING AVANDIA

[Storage conditions and expiry date]

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