

DATA SHEET

Avandia™ Film Coated Tablets

Rosiglitazone maleate

Presentation

Film coated, pentagonal shaped Tiltab™ tablets. The tablet strengths are distinguished by colour: 4.0mg (orange) and 8.0mg (red-brown).

Avandia 4.0mg tablets, orange in colour, are debossed with "GSK" on one side and "4" on the other. Each tablet contains 5.3mg rosiglitazone maleate equivalent to 4mg rosiglitazone.

Avandia 8.0mg tablets, red-brown in colour, are debossed with "GSK" on one side and "8" on the other. Each tablet contains 10.6mg rosiglitazone maleate equivalent to 8mg rosiglitazone.

Each strength is provided in opaque blister packs (PVC/aluminium).

Uses

Actions

AVANDIA, an antihyperglycaemic, is a selective and potent agonist at the PPAR γ (peroxisomal proliferator activated gamma) nuclear receptor and is a member of the thiazolidinedione class of antidiabetic agents. It improves glycaemic control by improving insulin sensitivity at key sites of insulin resistance namely adipose tissue, skeletal muscle and liver. Insulin resistance is known to play a major role in the pathogenesis of type 2 diabetes. Thus, AVANDIA improves metabolic control by lowering blood glucose, circulating insulin and free fatty acids.

As a consequence of different but complementary mechanisms of action, combination therapy of AVANDIA with a sulphonylurea or metformin resulted in synergistic improvements in glycaemic control in type 2 diabetic patients.

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

Consistent with the mechanism of action of AVANDIA, enhanced glycaemic control is accompanied by clinically significant decreases in serum insulin levels. There are also reductions in insulin precursors, which are believed to be cardiovascular risk factors. Significant decreases in free fatty acids are a key feature of AVANDIA treatment.

Pharmacokinetics

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

Administration of AVANDIA 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} (1.75 h) were observed compared to dosing in the fasted state. These small changes are not clinically significant and, therefore, it is not necessary to administer AVANDIA at any particular time in relation to meals. The absorption of AVANDIA is not affected by increases in gastric pH.

2. **Distribution:** The volume of distribution of AVANDIA is approximately 14L and total plasma clearance around 3L/h in healthy volunteers. Plasma protein binding of AVANDIA is high (approximately 99.8%) and is not influenced by concentration or age. There is no evidence for unexpected accumulation of AVANDIA after once daily or twice daily dosing.
3. **Metabolism:** Metabolism of AVANDIA is extensive with no parent compound being excreted unchanged. The major routes of metabolism are N-demethylation and hydroxylation, followed by conjugation with sulphate and glucuronic acid. The metabolites of AVANDIA are not considered to have any clinical relevance. *In vitro* studies demonstrate that AVANDIA is predominantly metabolised by CYP2C8, with a minor contribution by CYP2C9.

A study conducted in ten normal healthy volunteers showed that gemfibrozil (an inhibitor of CYP2C8) administered as 600 mg twice daily, increased rosiglitazone systemic exposure two-fold at steady state. Other CYP2C8 inhibitors have been shown to cause a modest increase in rosiglitazone systemic exposure (see Dosage and Administration, Warnings and Precautions, Interactions).

A study conducted in ten normal healthy volunteers showed that rifampicin (an inducer of CYP2C8) administered as 600 mg daily, decreased rosiglitazone systemic exposure by 65% (see Dosage and Administration, Warnings and Precautions, Interactions).

Since there is no significant *in vitro* inhibition of CYP1A2, 2A6, 2C19, 2D6, 2E1, 3A or 4A with AVANDIA, there is a low probability of significant metabolism-based interactions with drugs metabolised by these P450 enzymes. AVANDIA showed moderate inhibition of CYP2C8 (IC₅₀ 18µM)

and low inhibition of CYP2C9 (IC₅₀ 50µM) *in vitro*. An *in vivo* interaction study with warfarin indicated that AVANDIA does not interact with CYP2C9 substrates *in vivo*.

4. **Elimination:** Total plasma clearance of AVANDIA is around 3L/h and the terminal elimination half-life of AVANDIA is approximately 3 to 4 hours. There is no evidence for unexpected accumulation of AVANDIA 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 a 5-fold accumulation is anticipated.

Pharmacokinetics in special populations

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

Elderly: In the pooled population pharmacokinetic analysis, there were no marked differences in the pharmacokinetics of AVANDIA between elderly and non-elderly patients.

Hepatic Insufficiency: In patients with moderate to severe (Child-Pugh B/C) hepatic disease, unbound C_{max} and AUC were 2- and 3-fold higher in patients with hepatic impairment as a result of decreased plasma protein binding and reduced clearance of AVANDIA (see Posology and method of administration).

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

Indications

AVANDIA is indicated for the treatment of Type 2 diabetes mellitus (non-insulin dependent diabetes mellitus).

AVANDIA may be used as monotherapy in patients inadequately controlled by diet and exercise and in combination with sulphonylureas or metformin or where insulin is added to established AVANDIA to improve glycaemic control in patients with Type 2 diabetes mellitus.

AVANDIA may also be used in combination with both metformin and a sulphonylurea (triple combination therapy) to improve glycaemic control.

Dosage and Administration

AVANDIA therapy should be individualised for each patient.

AVANDIA may be taken with or without food.

Adults: The recommended starting dose for AVANDIA is 4mg/day. If patients require greater glycaemic control after 6-8 weeks of treatment, this dose can be increased to 8mg/day. AVANDIA dose adjustment may be needed when AVANDIA is co-administered with certain other drugs (see Warnings and Precautions, Interactions, Pharmacokinetics). AVANDIA may be given once or twice a day.

AVANDIA in combination with sulphonylurea

In combination with a sulphonylurea, the dose of AVANDIA should be initiated at 4 mg/day. Increases in AVANDIA to 8 mg/day should be undertaken cautiously following appropriate clinical evaluation to assess the patient's risk of developing adverse reactions relating to fluid retention (see Warnings and Precautions, Adverse Reactions).

Addition of insulin to patients receiving rosiglitazone therapy

For patients established on rosiglitazone receiving add-on insulin therapy, insulin must be titrated cautiously following appropriate clinical evaluation to assess the patient's risk of developing adverse reactions relating to fluid retention and other cardiovascular events (see Use with Insulin in **Warnings and Precautions, Adverse Effects, Clinical Studies – Cardiovascular Safety**).

AVANDIA should not be initiated in patients who already receive insulin.

Elderly: No dose adjustment is required in the elderly.

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

Impaired renal function: No dose adjustment is required in patients with mild and moderate renal insufficiency. Limited data are available in patients with severe renal insufficiency and therefore AVANDIA should be used with caution in these patients.

Impaired hepatic function: In patients with mild hepatic impairment (Child-Pugh A, scores of 6 or less) no dose adjustment is required. Owing to a difference in the pharmacokinetic profile (see Pharmacokinetic properties), AVANDIA is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B/C, scores greater than 6).

Contraindications

AVANDIA is contraindicated in patients with previous history of hypersensitivity to rosiglitazone or any other ingredient of the preparation (see List of Excipients).

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

Warnings and Precautions

Type I diabetes mellitus: AVANDIA is effective only in the presence of insulin and therefore should not be used in the treatment of type I diabetes mellitus.

Premenopausal anovulatory women: As a consequence of improving insulin sensitivity, AVANDIA treatment in premenopausal anovulatory patients with insulin resistance (eg. patients with polycystic ovary syndrome) may result in resumption of ovulation. These patients may be at risk of pregnancy.

Premenopausal women have received AVANDIA during clinical studies. Although hormonal imbalance has been seen in preclinical studies (see Preclinical safety data), no significant adverse experiences associated with menstrual disorders have been observed. If unexpected menstrual dysfunction occurs the benefits of continued therapy should be reviewed.

Renal impairment: No dose adjustment is required in patients with mild and moderate renal insufficiency. Limited data are available in patients with severe renal insufficiency and therefore rosiglitazone should be used with caution in these patients (see *Dosage and Administration, Pharmacokinetics*).

Hepatic impairment: In patients with mild hepatic impairment (Child-Pugh A, scores of 6 or less) no dose adjustment is required. Owing to a difference in the pharmacokinetic profile, rosiglitazone is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B/C, scores greater than 6) (see *Dosage and Administration, Pharmacokinetics*).

Cardiovascular: Rosiglitazone, like other thiazolidinediones can cause or exacerbate congestive heart failure in some patients.

AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated (see **Contraindications**). Patients and/or their carers should be warned of the potential symptoms of worsening cardiac function.

After initiation of AVANDIA, and after dose increases, patients should be monitored for signs and symptoms of heart failure (including excessive, rapid

weight gain, dyspnoea, and/or oedema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered.

Patients experiencing acute coronary syndromes (ACS) have not been studied in rosiglitazone controlled clinical trials. Since patients experiencing ACS are at an increased risk of developing heart failure, and in view of the potential for AVANDIA to cause or exacerbate heart failure, initiation of AVANDIA in patients experiencing an acute coronary event is not recommended. Furthermore, discontinuation of AVANDIA during the acute phase should be considered.

There is inconsistent evidence regarding the risk of cardiac ischaemia in patients treated with AVANDIA. A retrospective analysis of mostly short term integrated clinical trials (ICT) showed AVANDIA to be associated with an increased risk of myocardial ischaemic events in placebo-controlled but not active-controlled trials. This risk was not confirmed in individual large, longer duration studies comparing AVANDIA to metformin and sulphonylureas (see **Adverse Effects, Clinical Studies** – Cardiovascular safety).

Myocardial Ischaemia:

The use of AVANDIA is not recommended in patients with known ischaemic heart disease, particularly in those taking nitrates. AVANDIA has been shown to be associated with an increased risk of myocardial ischaemia (angina, infarction) in pooled short-term clinical studies, particularly in those who needed several antidiabetic drugs or nitrates. In a retrospective analysis of 42 clinical trials (mean duration 6 months), AVANDIA was associated with an increased incidence of myocardial ischaemia compared to combined active/placebo control (2.00% versus 1.53%, respectively). This risk was highest in patients for whom AVANDIA was added to established insulin therapy, and in patients receiving nitrates for known coronary heart disease (CHD).

Additionally, there is no conclusive evidence on the comparative effects of oral anti-diabetic drugs, including thiazolidinediones, on macrovascular risks and benefits in patients with type 2 diabetes mellitus.

Type 2 diabetes is a major risk factor for coronary heart disease and adverse outcomes following a myocardial ischaemic event. Thus, independent of the choice of anti-diabetic agent, cardiovascular risk factors should be identified and corrective measures taken where possible.

Use with Insulin:

AVANDIA should not be commenced as add-on therapy to patients already receiving insulin as part of their treatment regimen. There may be an increased risk of heart failure and myocardial ischaemia in this group (see **Adverse Effects**).

A small number of events typically associated with cardiac ischaemia have been observed with the addition of AVANDIA to patients already receiving insulin therapy and these events occurred at a higher frequency with the insulin plus rosiglitazone combination (2.77%) compared with insulin alone (1.36%). Therefore, AVANDIA is not recommended as add-on therapy to patients already receiving insulin (see **Dosage and Administration**).

In a separate study, where insulin was added to patients on established rosiglitazone-metformin therapy, there were no heart failure adverse events and one myocardial ischaemic event (angina) in the rosiglitazone-metformin plus insulin arm. In light of these data, for patients established on AVANDIA receiving add-on insulin therapy, insulin must be titrated cautiously following appropriate clinical evaluation to assess the patient's risk of developing adverse reactions relating to fluid retention and other cardiovascular events (see **Dosage and Administration, Clinical Studies** – Cardiovascular safety).

In patients who already receive the combination of AVANDIA and insulin, the discontinuation of this combination therapy should be considered in patients who develop any clinically significant fluid retention or other cardiovascular adverse events. Insulin therapy at appropriate doses is required in cases of inadequate therapeutic response to the combination.

Monitoring of liver function: In clinical trials with AVANDIA, encompassing 2492 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevations of ALT levels. In post-marketing experience with AVANDIA there have been rare reports of hepatocellular dysfunction, primarily evidenced by elevated hepatic enzymes. Causality has not been established.

Therapy with AVANDIA should not be initiated if patient exhibits clinical evidence of active liver disease or increased transaminase levels (ALT > 2.5 times upper limit of normal) at the start of therapy.

If a patient develops symptoms suggestive of 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 AVANDIA should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Eye Disorders: Very rare post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with rosiglitazone. Many of these patients reported concurrent peripheral oedema. In some cases the visual events resolved or improved following discontinuation of the drug. Prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity.

Hypoglycaemia: Patients taking rosiglitazone may be at risk of dose-related hypoglycaemia if receiving combination regimens that contain a sulfonylurea or insulin. A reduction in the dose of the concomitant agent may be necessary.

Bone Health: In a 4 to 6 year study of glycaemic control with monotherapy in recently diagnosed patients with Type 2 diabetes mellitus, an increased incidence of bone fracture was noted in female patients taking rosiglitazone (9.3%, 2.7 patients per 100 patient years) vs metformin (5.1%, 1.5 patients per 100 patient years) or glibenclamide (3.5%, 1.3 patients per 100 patient years). The majority of the fractures in the females who received rosiglitazone were reported in the upper arm, hand and foot. The risk of fracture should be considered in the care of patients, especially female patients, treated with rosiglitazone, and attention should be given to assessing and maintaining bone health according to current standards of care.

Administration with other drugs: Close monitoring of glycaemic control and AVANDIA dose adjustment may be needed when AVANDIA is co-administered with CYP2C8 inhibitors or inducers (**see Dosage and Administration, Interactions, Pharmacokinetics**).

Pregnancy and Lactation

Rosiglitazone has been reported to cross the human placenta and to be detectable in foetal tissues. There is no adequate data to support the use of AVANDIA during pregnancy or lactation in humans.

The use of insulin is generally recommended for patients with diabetes during pregnancy and lactation.

AVANDIA was not teratogenic in animal studies. There was no effect on the embryo during early pregnancy but treatment during mid-late gestation was associated with foetal death and retarded foetal development.

AVANDIA and/or its metabolites have been detected in the milk of lactating rats. It is not known if AVANDIA is secreted into human milk during lactation.

AVANDIA should be used during pregnancy and lactation only if the potential benefit justifies the potential risk to the foetus.

Effects on Ability to Drive and Use Machines

AVANDIA does not cause drowsiness or sedation. No effects on the ability to drive or operate machinery have been observed.

Other - Preclinical Safety Data

Consistent with other thiazolidinediones, AVANDIA inhibits ovarian oestradiol and progesterone synthesis and lowers plasma levels of these hormones resulting in effects on oestrous/menstrual cycles and fertility in animals.

There are no additional data of clinical significance.

Adverse Effects

Adverse drug reactions (ADRs) are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$) and very rare ($< 1/10,000$) including isolated reports. The frequencies of very common, common and uncommon events were determined from pooled safety data from a clinical trial population of >8,000 AVANIDA-treated patients.

Clinical trial data

Frequency categories have been assigned based on the differences in frequency between treatment and placebo or comparator groups rather than the absolute frequency, in order to estimate the portion of the ADRs which may be attributable to rosiglitazone. For dose-related ADRs, the frequency category reflects the higher dose of rosiglitazone. Frequency categories do not account for other factors including varying study duration, pre-existing conditions and baseline patient characteristics. ADR frequency categories assigned based on clinical trial experience may not reflect the frequency of adverse events occurring during normal clinical practice.

General disorders

oedema

rosiglitazone monotherapy vs. placebo	Common
rosiglitazone + metformin vs. metformin	Common
rosiglitazone + sulphonylurea vs. sulphonylurea	Very common
rosiglitazone + met + SU (triple therapy) vs. met+SU	Very common
rosiglitazone + insulin vs insulin	Very common

Oedema was generally dose-related, mild to moderate in nature and was more frequently observed when rosiglitazone was used in combination with a sulphonylurea or insulin.

Blood and lymphatic system disorders

anaemia

rosiglitazone monotherapy vs. placebo	Common
rosiglitazone + metformin vs. metformin	Common
rosiglitazone + sulphonylurea vs. sulphonylurea	Common
rosiglitazone + met + SU (triple therapy) vs. met+SU	Common
rosiglitazone + insulin vs insulin	Very common

Across all controlled clinical studies, decreases in haemoglobin and haematocrit (mean decreases in individual studies ≤ 1.0 g/dL and $\leq 3.3\%$, respectively) were observed for both AVANDIA alone and in combination with metformin or sulfonylurea. The changes occurred primarily during the first 4 to 8 weeks of therapy and remained relatively constant thereafter. Anaemia (decreased haemoglobin) was reported at an incidence of 1.9% in double-blind studies with AVANDIA. The incidence of anaemia was higher when AVANDIA was used in combination with metformin (7.1%) or with insulin

(8.6%). Lower pre-treatment haemoglobin/haematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anaemia in these studies.

Anaemia (reduction in haemoglobin) was generally dose-related and mild to moderate in nature.

White blood cell counts also decreased slightly in patients treated with AVANDIA. The observed changes may be related to the increased plasma volume observed with treatment with AVANDIA and have not been associated with any significant haematologic clinical effects.

Metabolism and nutrition disorders

hypercholesterolaemia

rosiglitazone monotherapy vs. placebo	Common
rosiglitazone + metformin vs. metformin	Uncommon
rosiglitazone + sulphonylurea vs. sulphonylurea	Common
rosiglitazone + met + SU (triple therapy) vs. met+SU	Common
rosiglitazone + insulin vs insulin	Common

Hypercholesterolaemia was reported in 3.4% of patients. The elevated total cholesterol levels were associated with an increase in both LDLc (n=2048) and HDLc (n=2177) and the ratio of total cholesterol:HDLc was unchanged or decreased in long term studies (n=886 after 12 months' therapy). Overall, these experiences were generally mild to moderate and usually did not require discontinuation of treatment. The elevated total cholesterol levels were associated with increase in both LDLc and HDLc and the ratio of total cholesterol:HDLc was unchanged in six month studies.

weight gain

rosiglitazone monotherapy vs. placebo	Common
rosiglitazone + metformin vs. metformin	Common
rosiglitazone + sulphonylurea vs. sulphonylurea	Common
rosiglitazone + met + SU (triple therapy) vs. met+SU	Common
rosiglitazone + insulin vs insulin	Common

Weight gain was generally dose-related-. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

hypoglycaemia

rosiglitazone + metformin vs. metformin	Uncommon
rosiglitazone + sulphonylurea vs. sulphonylurea	Common
rosiglitazone + met + SU (triple therapy) vs. met+SU	Very common
rosiglitazone + insulin vs insulin	Very common

Hypoglycaemia was generally mild to moderate in nature and was dose-related when rosiglitazone was used in combination with a sulphonylurea or

insulin. Patients receiving rosiglitazone in combination with insulin or oral hypoglycaemic agents may be at risk for hypoglycaemia, and a reduction in the dose of the concomitant agent may be necessary.

Cardiac disorders

congestive heart failure/pulmonary oedema

rosiglitazone + insulin vs insulin

Common

An increased incidence of heart failure has been observed when rosiglitazone (at both 4 mg and 8 mg) was added to treatment regimens that include sulphonylurea or insulin. Patients who experienced heart failure were on average older, had a longer duration of diabetes, and were mostly on the higher 8 mg daily dose of rosiglitazone. There were too few events to confirm a dose relationship; however, the incidence of heart failure appeared higher with 8 mg rosiglitazone compared to 4 mg rosiglitazone (total daily dose).

events typically associated with cardiac ischaemia

rosiglitazone + insulin vs insulin

Common

A higher frequency of events typically associated with cardiac ischaemia was observed when rosiglitazone was added to established insulin therapy (see **Warnings and Precautions, Clinical Studies** – Cardiovascular safety).

There is inconsistent evidence regarding the risk of cardiac ischaemia in patients treated with rosiglitazone. A retrospective analysis of mostly short term integrated clinical trials, showed rosiglitazone to be associated with an increased risk of myocardial ischaemic events in placebo-controlled but not active-controlled trials. This risk was not confirmed in individual large, longer duration studies comparing rosiglitazone to metformin and sulphonylureas. (see **Warnings and Precautions, Clinical Studies** – Cardiovascular safety).

In the retrospective ICT analysis described above, an increased rate of myocardial ischaemia serious adverse events (SAEs) was observed among rosiglitazone-treated patients who had received nitrates at baseline or received nitrates during the on-therapy trial period up to an event versus comparators. This finding has not been replicated in other long term clinical or epidemiological studies (see **Clinical Studies** – Cardiovascular safety).

Musculoskeletal, connective tissue and bone disorders

bone fractures

rosiglitazone monotherapy vs. metformin;

rosiglitazone monotherapy vs. glyburide/glibenclamide

Common

The majority of the fractures in the females who received rosiglitazone were reported in the upper arm, hand and foot (see **Warnings and Precautions**).

Postmarketing Data

Adverse drug reaction frequency categories were assigned based on reporting frequency of adverse events in the postmarketing setting with rosiglitazone irrespective of dose or concomitant antidiabetic therapy. Rare and very rare events were determined from post-marketing data and refer to reporting rate rather than true frequency.

Cardiac disorders
congestive heart failure/pulmonary oedema Rare

There have been post-market reports of serious adverse events, with or without a fatal outcome, potentially related to volume expansion (e.g. congestive heart failure, pulmonary oedema and pleural effusions) in patients receiving thiazolidinedione therapy.

Hepatobiliary disorders
hepatic dysfunction,
primarily evidenced by elevated hepatic enzymes Rare

A causal relationship to rosiglitazone has not been established. Hepatic abnormalities are known to be common in patients with diabetes. In a large clinical programme (4327 patients treated with rosiglitazone) the incidence of elevations of ALT greater than three times the upper limit of normal was equal to placebo (0.2 %) and less than that of the active comparators (0.5 % metformin/sulphonylureas). The incidence of all adverse experiences reports relating to Liver and Biliary systems also was low and equal to placebo (0.7%).

Skin and subcutaneous tissue disorders
angioedema Very rare
urticaria Very rare

Very rare post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with rosiglitazone (refer Precautions)

Interactions

Co-administration of therapeutic doses of AVANDIA had no clinically significant effects on the steady state pharmacokinetics or pharmacodynamics of other oral antidiabetic agents including metformin, glibenclamide, glimepiride and acarbose.

AVANDIA had no effects on the steady state pharmacokinetics of digoxin or warfarin nor did it affect the anti-coagulant activity of warfarin.

In vitro studies demonstrate that AVANDIA is predominantly metabolised by CYP 2C8, with CYP 2C9 as only a minor pathway.

Co-administration of AVANDIA with CYP2C8 inhibitors (eg. gemfibrozil) resulted in increased AVANDIA plasma concentrations (see Pharmacokinetics). Since there is a potential for an increase in the risk of dose-related adverse reactions, a decrease in AVANIDA dose may be needed when CYP2C8 inhibitors are co-administered.

Co-administration of AVANDIA with a CYP2C8 inducer (eg. rifampicin) resulted in decreased AVANIDA plasma concentrations (see Pharmacokinetics). Therefore, close monitoring of glycaemic control and changes in diabetic treatment should be considered when CYP2C8 inducers are co-administered.

Clinical data have shown that AVANDIA had no clinically relevant effect on the pharmacokinetics of S(-)-warfarin (a substrate for CYP 2C9).

No clinically relevant effects on nifedipine or oral contraceptives (components ethinylestradiol and norethindrone) were observed after co-administration with AVANDIA confirming a low probability of interaction with drugs metabolised by CYP 3A4.

Moderate ingestion of alcohol with AVANDIA has no effect on glycaemic control.

Overdosage

Limited data are available with regard to overdosage in humans. In clinical studies in volunteers AVANDIA has been administered at single oral doses of up to 20mg 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. AVANDIA is highly protein bound and is not cleared by haemodialysis.

Pharmaceutical Precautions

Shelf Life

Store below 30°C. Shelf-life at this temperature is 2 years.

Special Precautions for Storage

Nil

Medicines Classification

Prescription Only Medicine

Package Quantities

AVANDIA Tablets: 4mg, blister packs (PVC/aluminium) of 7 or 28

AVANDIA Tablets: 8mg, blister packs (PVC/aluminium) of 28

Further Information

List of excipients

Sodium starch glycollate, hydroxypropyl methylcellulose, microcrystalline cellulose, lactose monohydrate, magnesium stearate.

Film coat:

Opadry® yellow OY-L-22809

Opadry® pink OY-L-24802

Opadry® orange OY-L-23028

Opadry® pink OY-L-24803

Constituents of Opadry®:

Hydroxypropyl methylcellulose 6cP

Titanium dioxide E171

Polyethylene glycol 3000

Lactose

Triacetin

Iron oxide yellow E172

Iron oxide red E172

Purified talc

Clinical Studies

In clinical studies with AVANDIA given as monotherapy at doses of 4 to 8mg/day, the glucose lowering effects are gradual in onset and are not associated with hypoglycaemia. Reductions in fasting plasma glucose are observed from 1 week of initiation of therapy, although the full therapeutic effect may take 6-8 weeks to occur. Patients taking 8mg/day as monotherapy have experienced greater glycaemic control with AVANDIA given as a divided dose. Consistent with other anti-hyperglycaemic agents, improvement in glycaemic control with AVANDIA was associated with small increases in weight.

In type 2 diabetes, long term and sustained improvements in glycaemic control (FPG and HbA1c) have been demonstrated with AVANDIA given once or twice daily as monotherapy or in combination with other oral antidiabetic agents (sulphonylureas, metformin or insulin). In two studies, AVANDIA produced significantly greater reductions in fasting plasma glucose than glibenclamide after 52 weeks of treatment.

In two double-blind studies, AVANDIA in combination with insulin resulted in improved glycaemic control as well as a reduction in concomitant insulin dose.

AVANDIA administered in combination with metformin and glibenclamide (triple combination therapy) in two double-blind studies resulted in improved glycaemic control in patients inadequately controlled on glibenclamide and metformin combination therapy.

AVANDIA treatment has been associated with clinically significant reductions in fasting and postprandial plasma glucose levels and in glycated haemoglobin.

In controlled clinical trials, AVANDIA has been shown to increase the LDL cholesterol: apolipoprotein B ratio consistent with a beneficial change in LDL particle size from small dense LDL particles to larger more buoyant particles. This change has been confirmed by measuring LDL particle buoyancy (Rf) following 8 week treatment with AVANDIA in an open label study.

In a controlled clinical trial, AVANDIA (4 or 8 mg daily) used in combination with insulin and/or a sulphonylurea was effective in reducing glycaemia in patients with type 2 diabetes and mild to severe (not dialysis dependent) renal impairment. There were no additional safety concerns noted in these renally-impaired patients compared to type 2 diabetic patients without renal impairment.

In controlled clinical trials, AVANDIA has been shown to increase the LDL cholesterol: apolipoprotein B ratio consistent with a beneficial change in LDL particle size from small dense LDL particles to larger more buoyant particles. This change has been confirmed by measuring LDL particle buoyancy (Rf) following 8 week treatment with AVANDIA in an open label study.

Cardiovascular safety

Controlled clinical trials:

The RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) trial is a large, open-label, multi-year, prospective, controlled study in which patients with type 2 diabetes inadequately controlled with metformin or sulphonylurea were randomised to add-on AVANDIA or control. The median duration of diabetes in these patients was approximately 7 years. An interim analysis of this study is based on 4,447 participants with a mean follow up of 3.75 years, representing 16,675 patient-years of follow-up, which was approximately two-thirds of that intended by study completion. The adjudicated primary endpoint is cardiovascular (CV) hospitalisation (which included hospitalisations for heart failure) or CV death in rosiglitazone-containing treatments versus metformin plus sulphonylurea treatment. Although no definitive conclusions may be drawn before study completion, the interim analysis revealed no difference in the number of adjudicated primary endpoint events for AVANDIA (217/2220) versus control (202/2227) [Hazard ratio 1.08 (95% CI 0.89, 1.31)]. Similar number of events were observed in the AVANDIA group and the comparator group for the following adjudicated endpoints: myocardial infarction/sudden death (49 vs 45), CV death (29 vs 35), all cause death (74 vs 80), and the composite endpoint of CV death, myocardial infarction (MI) and stroke (93 vs 96). There were more patients with events of heart failure in the AVANDIA

group versus the comparator group (38 vs 17) [Hazard ratio 2.15 (95% CI 1.3, 3.57)].

In the ADOPT study, patients with any class of heart failure, unstable or severe angina, or uncontrolled hypertension were ineligible for the study. As there was a greater withdrawal rate for the glibenclamide group, it was important to depict the patient-year rates in addition to the incidence rates. A post-study adjudication of MI events and CV death was conducted by 2 external blinded cardiologists. The adjudicated MI event rate observed among patients on AVANDIA monotherapy (0.4 events per 100 Patient-Years; 1.4% of patients), metformin monotherapy (0.4 events per 100 Patient-Years, 1.2% of patients) and glibenclamide monotherapy (0.4 events per 100 Patient-Years, 1.0% of patients) was comparable. The number of adjudicated CV deaths in the AVANDIA group (0.12 events per 100 Patient-Years, 0.4%) was comparable to the metformin group (0.16 events per 100 Patient-Years, 0.6%) and fewer compared to the glibenclamide group (0.28 events Per 100 Patient-Years, 0.83%). The CHF SAEs were not adjudicated. For the AVANDIA group, the event rate (0.24 events per 100 Patient-Years, 0.8%) was comparable to the metformin group (0.24 per 100 Patient-Years, 0.8%); however, patients receiving glibenclamide experienced a lower rate of CHF events (0.07 per 100 Patient-Years, 0.2%).

In the retrospective ICT analysis of data from pooled clinical studies of short duration (median 6 months) the overall incidence of events typically associated with cardiac ischaemia was higher for AVANDIA containing regimens, 2.00% versus comparators, 1.53% [Hazard ratio 1.30 (95% CI 1.004 -1.69)]. Death from myocardial ischaemic events occurred in 0.15% on rosiglitazone-containing regimens and 0.12% on comparator regimens. Across the treatment regimens evaluated, the incidence rate of myocardial ischaemic events in AVANDIA and control treatment regimens was generally low. Further analysis revealed that this increase was observed in placebo-controlled trials but not active-controlled trials. The incidence of ischaemic events was higher in patients who received AVANDIA as add-on therapy to insulin and in patients receiving nitrates for ischaemic heart disease in this ICT database (see below):

- Rosiglitazone add-on to patients receiving insulin:

In the ICT analysis, a small number of events typically associated with cardiac ischaemia was observed when AVANDIA was added to patients on insulin and these events occurred at a higher frequency with the combination (2.77%) compared with insulin alone (1.36%). In this analysis, the overall incidence of events typically associated with heart failure was also higher when AVANDIA was added to insulin therapy (1.27%) versus continuation of insulin monotherapy (0.75%).

In a separate 24-week, controlled, randomised, double-blind trial of rosiglitazone and insulin co-administration, insulin was added to rosiglitazone-metformin (n = 161) and compared to insulin plus placebo (n = 158), after a single-blind 8-week run-in with

rosiglitazone-metformin. Patients with oedema requiring pharmacologic therapy and those with CHF were excluded at baseline and during the run-in period. No CHF was reported in either treatment group. In the group receiving rosiglitazone-metformin plus insulin, there was one myocardial ischaemic event (angina) and one sudden death. No myocardial ischaemia was observed in the insulin group.

- Rosiglitazone in patients on nitrates for ischaemic heart disease:

In the retrospective ICT database described above, an increased rate of myocardial ischaemia SAEs was observed among AVANDIA treated patients who had received nitrates at baseline or received nitrates during the on-therapy trial period up to an event (rosiglitazone 28 events/451 nitrate users; 6.2%) vs comparators (10 events/301 nitrate users; 3.3%). This finding has not been replicated in other clinical or epidemiological studies as described below:

In the ADOPT study described above, comparable rates of myocardial ischaemic SAEs were observed among treatment groups in patients who had received prior nitrates or had received nitrates during the on therapy trial period up to an event (rosiglitazone monotherapy 8 events/74 nitrate users; 10.8% vs. metformin 12 events/89 nitrate users; 13.5% vs. glibenclamide 9 events/76 nitrate users, 11.8%).

In a large observational balanced cohort study derived from the database of a large U.S. managed healthcare plan (Ingenix) patients receiving AVANDIA or other standard anti-diabetic agents (non thiazolidinediones) were well-matched for baseline characteristics and followed for an average of approximately one year. Subgroup analysis did not reveal an increase in the incidence of MI in patients receiving background nitrates for coronary heart disease (rosiglitazone-containing regimens [34.8 per 1000 person-years] vs. other anti-diabetic agents [55.9 per 1000 person-years] (see Observational studies below for details).

Observational studies:

A nested case-control study examined the odds of MI in type 2 diabetic patients exposed to the thiazolidinediones (rosiglitazone and pioglitazone, separately) as compared to diabetic patients exposed to other anti-diabetic therapies. The study used data from the Integrated Healthcare Information Services (IHCIS) healthcare claims database, which includes inpatient/outpatient and pharmacy claims on approximately 41 million enrollees. A total of 891,901 subjects identified from 1999 to 2006 were included in the study for analysis. The incidence rate of MI in the diabetic cohort was 0.53 per 100 person years. Compared to those treated with other anti-diabetic therapies, the adjusted odds ratio of MI was 1.02 [95% CI: 0.94-1.11] for rosiglitazone, 0.90 [95% CI: 0.82-0.98] for pioglitazone and 0.56

[95% CI: 0.53-0.59] for no anti-diabetic therapy. The likelihood of MI was the same for rosiglitazone compared to other anti-diabetic agents.

In the Ingenix study patients receiving rosiglitazone or other standard anti-diabetic agents (non thiazolidinedione) were well-matched for baseline characteristics and followed for an average of approximately one year. This study evaluated 33,363 type 2 diabetic subjects and assessed exposure-adjusted hazard ratios for a composite of hard CV endpoints (hospitalisation for MI and/or coronary revascularisation). The incidence rate of the composite endpoint of "MI and coronary revascularisation" was 1.75 events per 100 person years for rosiglitazone-containing regimens and 1.76 events per 100 person years for other anti-diabetic agents [Hazard ratio 0.93 (95% CI: 0.80 - 1.10)]. The incidence rate of MI was 0.80 events per 100 person years for rosiglitazone-containing regimens and 0.83 events per 100 person years for other anti-diabetic agents [Hazard ratio 0.92 (95% CI: 0.73 - 1.16)]. This study addressed coronary heart disease outcomes in rosiglitazone but not pioglitazone. A subsequent analysis in the same database included both thiazolidinediones, rosiglitazone and pioglitazone and followed subjects to the end of the first quarter of 2007. This study compared the risk of MI, coronary revascularisation and sudden death in 91,358 patients with type 2 diabetes who began rosiglitazone or pioglitazone. Follow-up was from start of therapy to the following three stopping points: 1. Major Change in Regimen; 2. Discontinuation; 3. Minor Change in Regimen. The summary hazard ratio for the combined cardiovascular outcome for rosiglitazone relative to pioglitazone was 1.01 [95% CI: 0.93-1.10] for follow-up through Major Change in Regimen, 1.02 [95% CI: 0.93-1.13] through Discontinuation, and 1.12 [95% CI: 0.97-1.29] up to Minor Change in Regimen. For MI, the respective hazard ratios were 1.19 [95% CI: 1.04-1.36], 1.21 [95% CI: 1.04-1.42], and 1.48 [95% CI: 1.16-1.88]. For coronary revascularisation, the corresponding hazard ratios were 0.99 [95% CI: 0.90-1.09], 1.02 [95% CI: 0.92-1.12], and 1.12 [95% CI: 0.97-1.31].

Another retrospective cohort study compared the risks of MI and coronary revascularisation among type 2 diabetic patients receiving rosiglitazone, pioglitazone, and other anti-diabetic agents. The study included 402,845 patients identified in the PharMetrics database compiled from over some 80 health plans in the U.S. and followed for 12-18 months. The overall incidence rate of MI was 0.46 per 100 person years for rosiglitazone-containing regimens, 0.44 per 100 person years for pioglitazone-containing regimens, and 0.41 per 100 person years for regimens containing all other anti-diabetic agents. The overall hazard ratio of MI comparing rosiglitazone to pioglitazone was 1.07 [95%CI: 0.89-1.27]. When rosiglitazone was compared to other anti-diabetic agents, the overall hazard ratio for MI was 1.06 [95% CI: 0.92-1.21]. Similarly, the overall hazard ratio of coronary revascularisation was 1.03 [95% CI: 0.93-1.14] comparing rosiglitazone to pioglitazone, and 1.01 [95% CI: 0.93-1.10] comparing rosiglitazone to other anti-diabetic agents. The overall hazard ratio of composite outcome of MI and/or coronary revascularisation was 1.04 [95% CI: 0.94-1.14] and 1.03 [95% CI: 0.95-1.11] when rosiglitazone was compared to pioglitazone and other anti-diabetic agents, respectively.

- ***Mild to moderate (NYHA class I and II) heart failure***

In a controlled echocardiographic study of 52 weeks duration, rosiglitazone was shown to be no worse than control for the change in ejection fraction from baseline to week 52 in 224 type 2 diabetes mellitus patients with NYHA Class I or II heart failure on oral background antidiabetic and heart failure therapy. Rosiglitazone did not affect mean echocardiographic structural and functional parameters. In this study, an independent committee conducted a blinded evaluation of eight fluid related or cardiovascular events according to predefined criteria (adjudication). The following adjudicated events occurred at a higher incidence in those patients treated with rosiglitazone compared with control: new or worsening oedema and/or dyspnoea (30% with rosiglitazone, 18% with control), worsening of heart failure (five (4.5%) patients with rosiglitazone, four (3.5%) with control), increase in heart failure medication use (which included diuretics; 33% with rosiglitazone, 18% with control) and cardiovascular hospitalisation (19% with rosiglitazone, 13% with control).

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