SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Avandia. This scientific discussion has been updated until 1 September 2003. For information on changes after this date please refer to module 8B.

1 Introduction

Rosiglitazone (RSG) is the active substance of the medicinal product Avandia. RSG is a novel thiazolidinedione antidiabetic agent thought to improve glycaemic control by improving insulin sensitivity. RSG acts as a selective and potent agonist at the nuclear receptor, peroxisomal proliferator activated receptor gamma (PPARγ).

Avandia is formulated as a film-coated immediate release tablet for oral administration. It contains the active ingredient rosiglitazone as the maleate salt in four dosage strengths 1 mg, 2 mg, 4 mg and 8 mg per tablet. The recommended initial oral dosage was 4 mg/day that could be increased if necessary to 8 mg/day after 8 weeks of treatment.

The clinical development program included studies in monotherapy and in combination, data from which were included in the Marketing Authorisation Application.

During the procedure of the original application, the efficacy of rosiglitazone in monotherapy was considered insufficiently documented. In a subsequent application in February 2003 additional data were submitted by the MAH on the use of rosiglitazone in monotherapy.

2. Chemical and pharmaceutical aspects

Composition

Avandia is formulated as film-coated immediate release tablets for oral administration. The tablet core contains rosiglitazone maleate (active substance), sodium starch glycollate (Type A), hypromellose 3cP, microcrystalline cellulose, lactose monohydrate, magnesium stearate. The film coating contains either Opadry yellow OY-L-22809, or Opadry pink OY-L-24802, or Opadry orange OY-L-23028, or Opadry pink OY-L-24803, which consists of hypromellose 6cP, titanium dioxide E171, macrogol 3000, lactose monohydrate, glycerol triacetate, iron oxide yellow E172, and/or iron oxide red E172 and purified talc (4mg tablet only).

Packaging material: The tablets are packaged in blisters containing 14 tablets in two rows of 7. The blister strips consist of a 250 µm laminate of opaque, white, polyvinyl chloride (PVC) and a 20 µm aluminium lidding foil.

Active substance

RSG is chiral and contains one asymmetric centre making 2 stereoisomers (enantiomers) theoretically possible. The active ingredient is presented as the racemate in Avandia, supported on the basis of preclinical studies and clinical efficacy and safety.

The synthesis and the in-process controls are satisfactorily described.

A number of amorphous and crystalline physical forms have been identified. The validation of the specifications and the analytical methods are acceptable and the specification for impurities is in conformity to the batch analysis as well as the requirements of ICH.

The impurity limits in the specification are considered qualified in view of the impurity levels observed in the batches used in safety and clinical studies. Batch analysis data are provided for 22 batches, reported against the proposed commercial specification and are satisfactory.

The proposed re-test period of 12 months for rosiglitazone maleate when stored in the commercial packaging material is acceptable and is supported by the provided stability data.

Other ingredients

All excipients are of pharmacopoeial quality, well established and suitable for pharmaceutical use. Magnesium stearate will be used in compliance with the amended Directive 75/318/EEC concerning

TSE. The MAH applied for a type I variation to replace magnesium stearate of animal origin with magnesium stearate of vegetable origin.

Product development and finished product

Development Pharmaceutics: Issues addressed in the development pharmaceutics section are composition, changes made during development, choice of excipients and compatibility, process optimisation, and tablet dissolution. The development pharmaceutics studies have been satisfactorily described.

Manufacturing process: The manufacturing process is in general satisfactorily described, and is standard for a product of this type. The process validation was performed on 3 pilot scale batches and the validation results are satisfactory. In addition, results from testing of one full-scale batch of each strength manufactured at the commercial manufacturing site are also provided. These batches were tested against the finished product specification, but no in-process parameters were addressed. The batches complied with the release specification; the content uniformity and dissolution data were acceptable. The manufacturing process has been satisfactorily validated.

Specifications of the medicinal product: The release and end of shelf-life specification for the finished products include tests for description, RSG identity and content, individual and total degradation products, dissolution, content uniformity, identity of colouring agents, and microbial quality. The test methods are suitable and satisfactorily described.

Batch analysis data: Batch analysis results are presented for 3 consecutive pilot scale batches of each strength manufactured at the commercial production site. The batches have been tested for all test parameters in the specification for the finished product except identification of colourants and microbial quality.

Stability of the medicinal product: The stability studies on the finished product were performed on 3 pilot scale batches of each strength manufactured by the commercial process at the commercial site. In view of the stability data provided, the requested shelf-life of 2 years for Avandia 1 mg, 2 mg, 4 mg and 8 mg tablets, when packaged in the commercial packaging material is considered acceptable.

3. Toxico-pharmacological aspects

Pharmacodynamics

The overall animal efficacy data supports both the potential antidiabetic effect of RSG in diseased individuals and the proposed clinical therapeutic regimen. RSG had an antidiabetic effect in several animal models of type 2 diabetes after repeated administration. The antidiabetic effect of RSG was maintained over a 30-week period in genetically diabetic mice and at least over 22 weeks in diabetic rats. In the Zucker rat, RSG had only a marginal effect on fasted glucose concentrations and showed no effect on HbA_{1C}-level when measured 9 months after treatment initiation. RSG was shown to be 10-fold more potent than pioglitazone or troglitazone as a glucose lowering agent in a mouse model for Type 2 diabetes. RSG showed an intermediate effect in the dietary normal obese rat, while no activity was observed in normoglycaemic animals or in models for insulin-dependent diabetes mellitus.

The antidiabetic activity of racemic RSG is predominantly due to the (S)-(-) enantiomer. One of the two identified human metabolites with significant *in vitro* binding affinity to PPARγ, sulphated para-hydroxylated RSG (M10), has an expected plasma AUC value considerably greater than parent RSG in man and a relatively longer plasma half-life. The enantiomers of RSG (ratio of 1:1) interconvert rapidly *in vitro* and *in vivo* where, in the used laboratory animal species, the S(-) form is favoured while in human, the R(+) form is the dominating enantiomer at equilibrium.

Interactions

Interaction between RSG and the antidiabetic agents glibenclamide (sulphonylurea), voglibose (α-glucosidase inhibitor) and human insulin was assayed in a 1-month toxicity study in rat. There was no evidence of other unexpected or synergistic effects arising from the combinations apart from the synergistic increase in brown fat weight observed upon co-administration with insulin or glibenclamide. In animals, RSG causes some induction of CYP4A and in the male rat only, CYP3A.

Although the preclinical results indicated that concomitant RSG-treatment may have an impact on the metabolism of carbamazepine, paclitaxel, or cerivastatin via inhibition of CYP2C8, and on oral contraceptives via potential induction of CYP3A, no clinically relevant interactions were observed in man (see clinical aspects). In addition, nonsteroidal anti-inflammatory drugs (NSAIDs) may activate PPARγ. The overall likelihood of significant metabolic interactions between RSG and other medicinal products metabolised by P450 enzymes is considered to be low.

Pharmacokinetics

Pharmacokinetic studies revealed overall similar qualitative kinetics in the pivotal species rat and dog compared with man, except that the relative total excretion rate in man was much slower than that of the rat and the dog, and the major route of excretion was via faeces (previously absorbed material) in the animals while urinary excretion dominated in man [3.9]. No metabolism data were reported for the mouse, although this species was used in several pivotal toxicity studies.[3.10] Whole-body autoradiography in pigmented rats revealed binding of RSG-related material to melanin-containing tissues (uveal tract and pigmented skin) with long terminal half-lives (40 and 60 days in uvea and skin, respectively). The potential for RSG-induced phototoxicity in patients is low based on an examination of available data relating to photostability, UV absorption and clinical observations.

Toxicology

Overall, qualitatively similar toxicity profiles were observed in mice, rat and dog, although the dog generally appeared to be more sensitive than the rodents.

Single dose toxicity: Single dose toxicity was performed in mouse (p.o. and i.v.), rat (p.o. and i.v.), and dog (p.o.). The animal species tolerated well a high single oral dose of RSG, the rodents being less sensitive than the dog. CNS related effects were the main observation in the rodents. In dogs, a decrease in erythrocyte parameters was observed at 20 mg/kg and emesis and weight loss at higher dosing (160mg/kg).

Repeated dose toxicity: Repeated oral dose toxicity of up to 12 months duration was performed in mouse rat and dog. In accordance with the animal efficacy studies RSG treatment had no effect on plasma glucose in healthy animals Few unscheduled deaths occurred (due to hydrothorax), and only at very high multiples of clinical exposure (40mg/kg/day) in the 6-month rat studies.

Toxicity profile in adipose tissue, heart, liver and pituitary gland/ovary: Increased fat mass comprising hyperplasia and transition of brown fat adipocyte tissue to white adipocyte tissue was observed at exposure levels below the maximum clinical exposure. At higher exposures, increased fat content was also observed in bone marrow of rat and dog. These effects are considered to be a result of the pharmacological action of RSG. Cardiovascular safety pharmacology studies revealed significant increase in heart rate, cardiac output and stroke volume, with slight reductions in blood pressure and a significant reduction in total peripheral resistance, concomitant with increased heart weight. Increased heart weight not associated with ECG changes was observed in all species, at clinical exposure in dog. The sensitivity to cardiac hypertrophy increased with treatment duration. Further cardiovascular effects observed were plasma volume expansion and decrease in erythrocyte parameters; red cell mass was normal or slightly increased. In the rat and the dog a progressive increase over time was observed in blood flow in adipose tissue, and to a lesser extent in skin and (in dog) in the small intestine. Furthermore, RSG-treatment was found to cause an early and sustained antinatriuretic effect. The cardiovascular effects were believed by the applicant to be mediated by the following cascade: increased regional blood flow and reduced total peripheral resistance induce sodium and water retention in the kidney and result in increased plasma volume, increased preload and adaptive cardiac hypertrophy.

Increased liver weight was observed in rats and in dogs but not in mice. In the dog, liver weights were increased at clinical exposure levels. Additional effects observed only in the dog were a significant increase in plasma ALT and ALP, brown pigmentation containing iron (haemosiderin), increases in liver non-haeme iron content and lipofuscin, increases in cell proliferation (PCNA labelling index) and in cell density. The species sensitivity to hepatotoxicity correlated with the degree of oxidative cleavage metabolic pathway of RSG, which was 23-32% in dog and 7-17% in rat (human 4%). *In vitro* studies with potentially suspected metabolite moieties associated with oxidative stress cleavage

pathway did not reveal conclusive results. RSG did not induce liver tumors in mice or rats treated for 2 years.

Additional toxic events associated with prolonged RSG treatment were: (i) increase in mean pituitary weight along with hyperplasia of prolactin-containing cells of the pars distalis in female rats (not in dogs); (ii) reduction of ovary weight in female rats at high doses associated with a reduction/absence of corpora lutea; (iii) reduction in platelet count in mouse and rat but not in dog.

Reproduction toxicity: RSG was not teratogenic in rat and rabbit. Significant toxicity on fertility observed in high-dosed rat females consisted of disruption of oestrous cycles and placental pathology findings including increased weight, delayed maturation, basal zone degeneration and labyrinth congestion/necrosis. Increased pre- and post-implantation loss, reduced embryo/foetal viability and growth were also noted in the high-dose group of animals. No similar toxicity was noted in the rabbit except increased pre and implantation loss and decrease in foetal weight at high doses. RSG was found *in vivo* to reduce plasma levels of oestradiol and progesterone in the rat as well as in the Cynomolgus female monkey. The LOAEL for effects on the menstrual cycle in monkeys was only at 2-fold the high (average) therapeutic AUC and 3-fold clinical C_{max}. For effects on the placenta, embryo-foetus and offspring the no-effect level was 4-fold clinical systemic exposure.

Mutagenicity: RSG was not mutagenic or clastogenic in the *in vitro* bacterial assays for gene mutation, the *in vitro* chromosome aberration test in human lymphocytes, the *in vivo* mouse micronucleus test, and the *in vivo/in vitro* rat UDS assay. There was weak mutagenic activity *in vitro* in the mouse lymphoma test in the presence of metabolising system at moderately cytotoxic concentrations above 50-100 μM.

Carcinogenicity: In the submitted documentation, RSG showed no carcinogenic potential in mice while in rats an increased incidence of benign subcutaneous lipomas (3-4 fold above control) was observed in mid-dose male and high-dose female animals. In the males, the lowest observed adverse effect level was estimated to be 1.8x for both clinical C_{max} and AUC. The increase in adipocyte hyperplasia is probably due to persistent pharmacological overstimulation of adipocytes. Due to the absence of a sufficient margin of exposure to the human dose, the appearance of benign lipomas upon prolonged treatment with RSG in patients cannot be excluded. Moreover, the animals may not have been adequately exposed to the main human metabolite, recently found to be active *in vivo*.

There has been a report in the literature that in an animal model for familial adenomatous polyposis (FAP), treatment with RSG at 200 times the pharmacologically active dose and with troglitazone, increased tumour multiplicity in the colon. The relevance of this finding is unknown. However, RSG and troglitazone promoted differentiation and reversal of mutagenic changes in human colon cancer cells *in vitro*. As outlined above, RSG was not mutagenic in the standard battery of genotoxicity tests and there was no evidence of colon tumours in the two lifetime rodent carcinogenicity studies with RSG. This information has been included in the SPC.

Special toxicity studies: Passive cutaneous (PCA) and active systemic anaphylaxis tests (ASA) were carried out in guinea-pigs, the former test including determination of mast cell binding antibodies (IgE/IgG_{1b} and IgG_{1a}) after sensitisation. There were no reactions or antibody productions associated with administration of RSG, nor did RSG induce antigenic responses in the rat PCA model.

Ecotoxicity/Environmental Risk assessment: According to a phase I environmental risk assessment, the use of projected production levels (8750 kg/year for the EU market) will not have a negative impact on the environment.

GLP Status: All toxicity studies were conducted in compliance with the GLP principles.

4. Clinical aspects

Clinical pharmacology

The clinical pharmacology program referred to:

- The safety, tolerability and pharmacokinetics following either single doses of up to 20 mg, or repeat doses up to 8 mg/day, or single intravenous doses up to 4 mg in healthy volunteers and special populations (elderly, obese, hepatic impairment, renal insufficiency).

- The absorption, distribution, metabolism, excretion and absolute bioavailability of a single dose of RSG in healthy volunteers.
- The potential drug interactions including other oral antidiabetic agents, digoxin, warfarin, cytochrome P450 3A4 substrates and H_2 receptor antagonists.

Pharmacodynamics

As expected from the proposed mechanism of action, single oral or intravenous doses of RSG up to 20 mg did not induce significant changes in blood glucose in healthy volunteers. For glucose lowering effects in diabetic patients, more importance should be given to the clinical trials since the pharmacology trials were not powered to detect statistically significant differences in glucose concentrations.

Pharmacokinetics

A total of 533 healthy volunteers, patient volunteers and patients with type 2 diabetes participated in a clinical pharmacology program consisting of 24 studies. The pharmacokinetics of RSG have been extensively studied and well documented after single dose administration up to 20 mg and repeat doses up to 8 mg/day in a total number of 494 subjects.

Following administration in the fasted state, RSG was rapidly and completely absorbed. Maximum plasma concentrations were reached about 1 hour after dosing at all dose levels. The pharmacokinetic parameters of RSG are proportional to dose in the dose range 1 to 8 mg. The absolute bioavailability was 99%. Based on absorption data RSG can be taken without regard to food as the rate, but not the extent of absorption was influenced by food. RSG is mainly distributed to the extracellular water (V_D 16 L), is highly bound to plasma proteins (99.76%), and has a low clearance (3.4 L) and an elimination half-life of 3 to 4 hours. RSG is almost completely metabolised with no unchanged parent compound excreted in the urine. The major routes of metabolism are N-demethylation and hydroxylation followed by conjugation with sulphate and glucuronic acid. RSG is predominantly metabolised by the cytochrome P450 iso enzyme CYP2C8, with CYP2C9 representing only a minor pathway. 65-69% of the dose is excreted via the urine and 25% in faeces. The elimination of total radioactivity from plasma was very slow, with a half-life of about 150 h. The major metabolite in plasma is sulphated para-hydroxylated RSG (M10). The predicted exposure (AUC) to M10 is approximately 22-fold higher than RSG at steady-state, while the unbound exposure is expected to be less or similar to that of RSG as the protein binding of M10 is very high (>99.99%). Although the bulk of the data indicates that RSG clearly contributes to the pharmacological activity, the possibility that the main metabolite M10 may contribute to the effect cannot be ruled out. However this is not considered to raise safety concerns, as stated in the SPC.

Interaction studies

RSG is expected to cause mild inhibition of CYP2C8, but no significant inhibition of the other isoenzymes. No clinically relevant interactions were observed in the *in vivo* drug interaction studies which included other oral antidiabetic agents (glibenclamide, metformin, acarbose), cardiovascular medicines with narrow therapeutic indices (digoxin and warfarin), CYP3A4 substrate (nifedipine), oral contraceptives and ranitidine. Any possible influence of other drugs metabolised by CYP2C8 on the pharmacokinetics of RSG has not been studied. Cerivastatin is expected to have a low potential for interaction with the metabolism of RSG, while paclitaxel may inhibit the metabolism of RSG. The interaction potential of the major metabolite M10 is low.

Clinical efficacy

Efficacy was studied with RSG as monotherapy and in combination with SU and metformin. Once daily and twice daily regimens were evaluated. An overview of the performed double blind trials is given in Table 1. The clinical studies conform to the essential principles of Good Clinical Practice. Further information regarding long-term efficacy and safety was provided from six open label extension (OLE) studies and from one open label, active comparator, cardiac safety study of 12 months duration. The appeal documentation submitted in December 1999 included results from OLE

studies with patients exposed to rosiglitazone for greater than 24 months. In the course of the evaluation, data referring to safety only were submitted from clinical trials using RSG in combination with insulin.

The subsequent submission in February 2003 presented additional data on the use of RSG as monotherapy, including results from OLE studies with patients exposed to rosiglitazone monotherapy up to 3 years.

Dose-response studies and main clinical studies

- **Dose response studies**

Three double-blind, placebo-controlled trials were conducted in patients with type 2 diabetes (Table 1); one for a duration of 12 weeks (006) and two for 8 weeks (090, 098). The aim of the studies was to investigate the lower and upper portion of the dose-response curve for Fasting Plasma Glucose (FPG).

- **Main studies**

Description of the studies

The performed studies to support efficacy are indicated in table 1.

Table 1: Overview of double-blind studies presented in the MAA

Study No.	Duration	RSG total daily dose (regimen)	Treatment Groups	Site	N (ITT)
Dose-response studies					
006	12 weeks	0.1-4 mg (bd)	RSG, placebo	US	380
090	8 weeks	4-12 mg (bd)	RSG, placebo	US	284
098	8 weeks	4-12 mg (od)	RSG, placebo	Europe	369
Monotherapy Studies					
011	26 weeks	4,8 mg (bd)	RSG, placebo	US	493
024	26 weeks	4,8 mg (od) 4,8 mg (bd)	RSG, placebo	US	908
020	52 weeks	4,8 mg (bd)	RSG, GLB titration (2.5 to 15 mg)	Europe	587
Combination with SU					
015	26 weeks	2,4 mg (bd)	(GLB, glipizide or gliclazide) + (RSG or placebo)	Europe	574
079	26 weeks	4 mg (bd)	GLB+placebo, RSG+placebo, RSG+GLB	US	296
096	26 weeks	2,4 mg (od)	GLB + RSG GLB + placebo	US	346
Combination with MET					
093	26 weeks	8 mg (bd)	MET+placebo, RSG+placebo, RSG+MET	US	306
094	26 weeks	4, 8 mg (od)	MET + RSG MET + placebo	US	339

Abbreviations: bd: twice daily; od: once daily; GLB: glibenclamide; MET: metformin

Patient population

All patients had a diagnosis of type 2 diabetes mellitus according to the National Diabetes Group definition. In US studies, FPG prior to randomisation had to be 7.8-16.7 mmol/L. In the European studies FPG had to be 7-15 mmol/L as per the new WHO diagnostic definition of diabetes. Men and women, aged 40-80 could be included if they did not have diabetic complications requiring treatment, or serious renal, hepatic or haematological impairment, or severe (NYHA class III or IV) heart failure. Prior to study entry, patients were either managed by diet and exercise but had developed a requirement for oral hypoglycaemic therapy, or were already taking oral antihyperglycaemic agents. In the main monotherapy studies any previous antihyperglycaemic medication was withdrawn 6-8 weeks before randomisation.

Efficacy parameters

For all Phase III trials, the primary endpoint was change of the HbA_{1c} concentration at the end of the treatment period compared to baseline. The primary comparisons were between the RSG and control groups. Secondary assessments of efficacy were also presented as change from baseline of the plasma levels of: FPG, fructosamine, lipids (total cholesterol [TC], HDL-cholesterol [HDLc], LDL-cholesterol [LDLc], VLDLc, triglycerides, free fatty acids [FFAs]), insulin and C-peptide. Insulin precursors, postprandial glycaemia and apolipoproteins A_I (Apo AI) and B_{100} (Apo B) were also measured in selected studies. HbA_{1c} responders were prospectively defined as patients who had ≥ 0.7% decrease in HbA_{1c} compared to baseline. FPG responders were prospectively defined as patients who had ≥ 30 mg/dl (1.7 mmol/L) decrease compared to baseline. The proportion of patients who achieved a target FPG of < 140 mg/dl (7.8 mmol/L) was also assessed (target based on National Diabetes Group diagnostic criterion).

Statistical analysis

The primary efficacy analyses were performed based on the Intention To Treat (ITT) population, which was defined as all randomised patients who had at least one valid observation for an efficacy variable while on treatment. For withdrawn patients or missing values during the double-blind period, LOCF (Last Observation Carried Forward) was used, which is considered acceptable in this therapeutic area.

RESULTS

Study populations

The mean age of patients, proportion of men and women, mean BMI (Body Mass Index) and distribution of races were similar across all treatment groups. Patients < 65 years old represented two thirds of the population and few patients were >75 years old. As would be expected, patients receiving RSG or placebo as monotherapy had a shorter mean duration of type 2 diabetes than patients receiving RSG in combination with SU or metformin (5.7 and 5.6 years compared with 8.7 and 7.5 years respectively). Baseline levels of HbA_{1c} and FPG, were similar for all treatment groups in all individual trials. The Phase III placebo-controlled trials evaluated a population with mixed experience of prior antidiabetic therapy, approximately 30% had not received oral anti-hyperglycaemic medication previously.

Patient disposition: A total of 3,120 patients out of 4,327 (72%) who received RSG either completed the study or completed the study and were reported as being on study in OLE studies, compared with 65% of those who received placebo and 75% of those who received an active comparator. Withdrawals due to adverse events (AEs) were comparable in the three groups.

Efficacy results

Phase II trials established a dose-response relationship on FPG for RSG within the recommended dosage range. Eight mg/d appeared to be the maximally effective dose. Subgroup analyses indicated similar dose-response curves for male and female patients.

Effects on HbA_{1c} and FPG:[4.10]

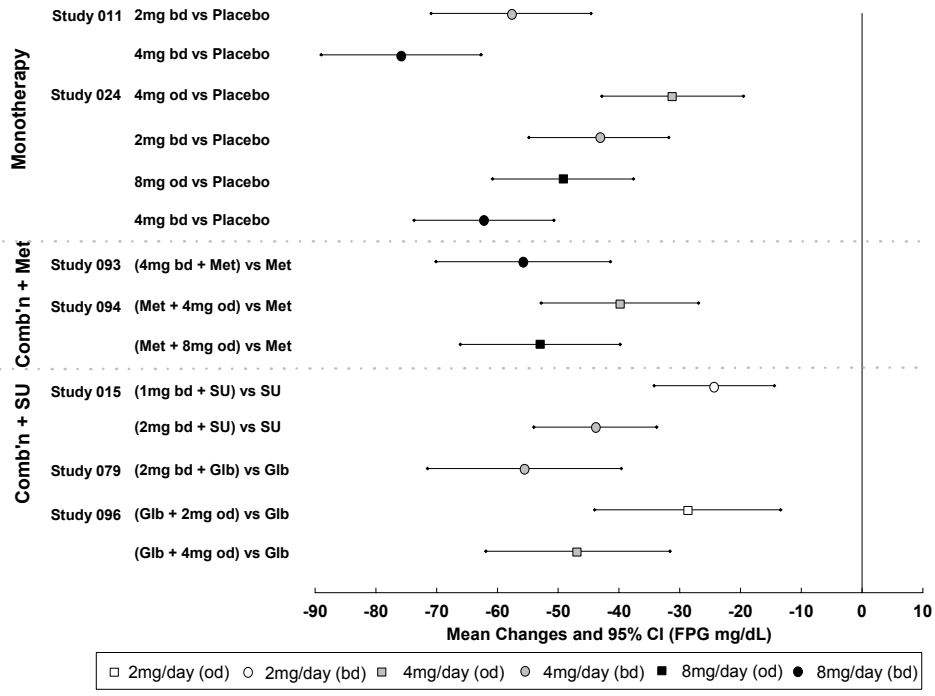
Monotherapy

The mean effect of RSG compared with placebo on HbA_{1c} in two 26-week monotherapy studies was –1.2% (CI: -1.5, -0.9) and –0.93% (CI: -1.2, -0.6) with the 2 mg dose twice daily and –1.5% (-1.9, -1.2) and –1.45% (CI: -1.8, -1.1) with the 4 mg twice daily. Generally, 8 mg/d appeared more effective than 4 mg/d and twice daily dosing more effective than once daily dosing, but statistically significant differences between dose levels and regimens were not demonstrated. RSG monotherapy given once or twice daily was significantly superior to placebo regarding change from baseline in HbA_{1c} and FPG. The response rate, based on reduction of HbA_{1c} of $\geq$ 0.7% was 28-54% in the treatment groups and 6-9% in the placebo groups. Similar responses were obtained on the FPG criteria (Fig 1).

In the 52-week monotherapy study vs glibenclamide (median dose 7.5 mg/d after an initial 12-week period of dose-titration), the effect was –0.27% (CI:-0.42, -0.12) and –0.53% (CI: -0.72, -0.34) with the 2 and 4 mg twice daily dose respectively. The effect of glibenclamide in this study was –0.72% (CI: -0.86, -0.58). These results fulfilled the protocol-defined criteria for non-inferiority of RSG 4 mg twice daily compared with glibenclamide for change from baseline in mean HbA_{1c} after 52 weeks. Compared with glibenclamide, the onset of action of RSG was slow, with a near maximum effect on HbA_{1c} reached after 16 weeks, compared with 8 weeks for glibenclamide. In subgroup analyses, efficacy of RSG was better in anti-diabetic medication naive patients compared with patients with previous experience of anti-diabetic medication.

In a subsequent application the MAH submitted additional data on the use of rosiglitazone as monotherapy. This included data to assess the non-inferiority of rosiglitazone to metformin on glycaemic control at 18 months. The data were considered satisfactory to support approval. These data formed an interim analysis of an ongoing study, and will be discussed in detail only when the full study has completed, to ensure the integrity of the ongoing blinded study

Figure 1: FPG: Change from Baseline



Although not designed for this purpose, combination trials 093 and 079, which included monotherapy arms with RSG, provided some insight regarding efficacy of RSG monotherapy in patients insufficiently controlled on monotherapy with glibenclamide or metformin. In both trials, RSG monotherapy was inferior to continued monotherapy with the comparator regarding metabolic control at study end.

Combination therapy

In combination trials, RSG, 2-4 mg/d together with adequately dosed SU and 4-8 mg/d in combination with submaximal doses of metformin, produced significant add-on efficacy on HbA_{1c} and FPG, of a magnitude similar to that found in placebo-controlled monotherapy trials. This is in line with the different mode of action of RSG. Compared with SU + placebo (background SU therapy either glibenclamide, glizipide or gliclazide) the effect of combination with 2 mg RSG bd on HbA_{1c} was –1.0% (CI: -1.3, -0.8), and –1.4 (CI: -1.73, -1.07), in a further study the effect of 4 mg od was –0.8 (CI: -1.1, -0.6). In the metformin combination studies (metformin 2.5 g/d) the effect of 4 mg RSG od over metformin alone was –0.97 (CI: -1.32, 0.63), of 8 mg od –1.18 (CI: -1.53, -0.83) and of 4 mg bd -0.8 (CI: -1.2, -0.5). Similar responses were obtained in the FPG criteria (Fig.1).

Effects on post-prandial glycaemia:

RSG monotherapy was assessed in a subset of 89 patients in a placebo-controlled trial. At all doses of RSG postprandial $AUC_{glucose}$ decreased significantly compared to placebo. Consistent results were seen at 12 weeks in 60 patients receiving 8mg RSG.

Effects on insulin and insulin-precursors:

RSG in monotherapy decreased serum levels of insulin and insulin-precursors significantly and in a dose-dependent manner.

Effects on lipids:

RSG 4 mg and 8 mg daily reduced FFAs in a dose-dependent fashion both in monotherapy and in combination. Effects on TG levels appear neutral during long-term therapy in the presented population. RSG increased TC, HDLc and LDLc in a statistically significant and dose-dependent fashion. This was observed both in the monotherapy studies and in the combination therapy groups in the combination studies (Table 2).

Table 2: Changes in Total Cholesterol, HDLc and LDLc at 26 weeks in double-blind Studies (ITT with LOCF)

	Total Cholesterol (mg/dL)	HDLc (mg/dL)	LDLc (mg/dL)	TC:HDLc ratio
4mg/day				
N*	1240	1237	1168	1237
Baseline mean	214.6	44.9	129.0	5.08
Mean change	+ 22.9	+ 3.6	+ 12.8	- 0.19
8mg/day				
N*	941	940	880	940
Baseline mean	212.0	44.7	124.5	5.04
Mean change	+ 29.6	+ 5.6	+ 19.4	- 0.24

* N = number of patients for whom change in parameter could be calculated on LOCF basis.

Most of the increase in LDLc appears to have occurred during the first four weeks. During long-term therapy (> 12 months) the early increase in LDLc levels off, whereas HDLc rises progressively and continuously over the study period. The HDLc increase was, however, not accompanied by an increase in ApoA1. Additional detailed data on the effects of RSG combination therapy on the lipid profile were submitted for a duration of 18 months. The TC:HDLc and LDLc:HDLc ratios remained unchanged or showed a slight trend for improvement beyond one year of therapy. The clinical relevance of these changes is unknown.

Clinical studies in specific populations

Target population: A wide range of type 2 diabetes patients was represented in the clinical trials. The population pharmacokinetic analysis showed that no dose alterations are required on the basis of gender, weight, age, race, smoking or alcohol consumption.

Patients with impaired renal function: Patients with mild, moderate and severe renal impairment showed only slightly higher unbound C_{max} and AUC (up to 19%) than subjects with normal renal function. Therefore no dosage adjustment is needed in renal impairment. There is no information regarding the excretion or additional accumulation of metabolites in renal impairment. However,

safety data indicate that patients with mild and moderate renal impairment did not have an increased incidence of adverse events compared with patients with normal renal function. The experience with RSG is limited in severe renal impairment. Therefore, RSG is recommended for use with caution in these patients.

Patients with impaired liver function: In liver impairment (Child-Pugh B), the unbound C_{max} and AUC were 2- and 3-fold higher than in healthy volunteers. The variability in unbound AUC within patients with moderate liver impairment was very high and only two patients with mild hepatic impairment were included in the study. Thus, the pharmacokinetic information in patients with mild, moderate and severe hepatic impairment is too limited to make a dose recommendation. Therefore, RSG is not appropriate for use in any patients with hepatic impairment.

Children: The efficacy and safety of RSG has not been studied in children and adolescents. Therefore, its use is not recommended in these age groups.

Post-hoc analysis in specific subgroups of patients

In specific diabetic populations who cannot tolerate the combination of SU+metformin, an unmet medical need is present. The only alternative option in this situation is insulin, whereas this therapy requires more frequent blood measurements with a risk of hypoglycaemia which makes this therapy less appropriate in certain patient groups. Also insulin is less appropriate in cases with severe insulin resistance. The applicant provided supplementary information to support the possible use of RSG in such populations, specifically

(i) in combination with metformin in obese patients

(ii) in combination with SU in patients who show gastrointestinal intolerance to metformin or in whom metformin is contraindicated.

(i) In combination with metformin in obese patients. The administration of an insulin secretagogue such as SU cannot be recommended in obese patients insufficiently controlled on metformin because most of these patients are markedly insulin-resistant and have high insulin levels. These patients may benefit from an insulin sensitiser. In the file data were provided on 162 obese patients (defined as BMI > 30 kg/m^2) treated with RSG + metformin. Analyses of this subgroup indicated no differences in efficacy and safety up to 18-months between the obese patients and the overall population included in the principal studies for combination of RSG and metformin. In fact, patients with BMI > 30 kg/m^2 showed a greater efficacy regarding reduction of insulin resistance from baseline compared to patients with a BMI < 30 kg/m^2. Weight in obese patients on combination therapy was increased (on average 2.6% weight gain) compared to the known and observed weight loss in the metformin alone group.

(ii) In combination with SU in patients who show gastrointestinal intolerance to metformin. Up to 15% of diabetic patients show gastrointestinal intolerance to metformin. However, it is not expected that patients intolerant to metformin will have a different response regarding glucose control by RSG. Data for patients intolerant to metformin were not available. However, data were submitted showing that there were no differences in efficacy and safety of RSG added to metformin in 114 patients who had metformin related gastrointestinal adverse events (but continued on metformin) compared to patients without gastrointestinal disturbances. Since RSG does not induce gastrointestinal adverse events, it can be assumed that it can be safely used in metformin intolerant patients.

In combination with SU in patients in whom metformin is contraindicated. Due to the risk of lactic acidosis metformin is contraindicated or not recommended in patients with renal failure or the very elderly. In the file, data were presented on 396 patients (274) patients with mild/moderate renal insufficiency and 122 patients >70 years. There were no differences in the efficacy and safety compared with the overall population in the principal studies for oral combination of RSG + SU.

Discussion on efficacy

(i) In the initial MAA clinical trials results provided insufficient evidence of efficacy for RSG in monotherapy, because no adequate comparison to metformin was provided and the trial vs glibenclamide may not have allowed for optimal use of glibenclamide for the whole duration of

the study. Subsequently, data were submitted to support the use of RSG as a second line monotherapy. The data were considered satisfactory and use as second-line monotherapy was granted once the first-line status of metformin was acknowledged and the indication was clear that rosiglitazone is an alternative for patients for whom metformin would otherwise be the first alternative.

The data presented for rosiglitazone in monotherapy did not suggest that hypoglycaemic efficacy or short- to medium-term safety are dependent on obese or non-obese status. However, it should be noted that the overall database for rosiglitazone assessed during the MAA warranted the following statement in the approved SPC (section 5.1): "A more pronounced glucose-lowering effect was observed in obese patients." Considering the currently approved indication for combination therapy, as well as the pharmacological activity of insulin sensitisers, the CPMP was of the opinion that the use of rosiglitazone in second line monotherapy should be further clarified by using a weight qualification.

(ii) As a combination therapy with metformin or SU, RSG was compared to placebo. RSG was effective in reducing HbA_{1C}. However, RSG has not been compared to the widely used SU+metformin combination. Hence, it is not known whether the combination of RSG with metformin or SU offers any advantages regarding efficacy compared to the standard combination. Therefore, a marketing authorisation for the combination in the indication "RSG is indicated for use in combination with sulphonylureas or metformin in patients who are not satisfactorily controlled by either agent alone" cannot be granted until the data from a comparative study are submitted and assessed.

(iii) Among the patients insufficiently controlled on monotherapy with one of the currently approved oral antidiabetics, there is a subgroup of patients for whom the SU+metformin combination is not an option. Currently the available therapy for these patients would be insulin, and insulin therapy is associated with practical problems in particular in elderly patients as well as with the risk of hypoglycaemia. Specifically, satisfactory data were submitted to support the use of RSG

a) in combination with SU in patients who are not satisfactorily controlled upon monotherapy and show gastrointestinal intolerance to metformin or where metformin is contraindicated.

b) in combination with metformin in obese patients who are not satisfactorily controlled upon metformin monotherapy. In order to harmonise the indication for combination therapy with the monotherapy indication, the weight qualification was subsequently amended from obese to overweight patients. These patients may generally be expected to exhibit marked insulin resistance and would benefit from therapy with an insulin sensitiser.

Therefore, the use of RSG can be recommended for these subgroups of patients for whom an unmet medical need is present.

Clinical safety

In the Phase II/III clinical trial program of the initial application, safety of RSG was assessed in 5,479 patients with Type 2 diabetes in 19 studies conducted in Europe and USA (5,042 patients in integrated database, 437 patients in ongoing echocardiographic studies). The clinical cut-off for the integrated database was 18 June 1998. Additionally, all Serious Adverse Events (SAEs) and deaths occurring in clinical studies after the clinical cut-off were included up to 05 November 1998.

The appeal documentation provided additional patient years of exposure in all groups (Table 3), reflecting the increased duration of exposure rather than entry of new patients into the studies or of new studies. The updated safety database includes over 1,000 patients treated with RSG for at least 2 years and 2,000 patients treated for at least 1 year, of whom 897 patients were treated in combination with SU or metformin. Furthermore, data from the post-marketing experience in the U.S.A. were submitted.

Table 3: Patient Years of Exposure for the MAA* and Safety Update Databases

	Patient Years of Exposure		
	MAA	First Safety Update	Second Safety Update
	CCO* 18/06/98	CCO 05/11/98	*Data available on 05/11/99*
RSG + SU	552	774	1042
RSG + MET	272	403	646
RSG monotherapy	1668	2496	3334

*MAA: marketing authorisation application; CO = clinical cut-off

other abbreviations see Table 1

In a subsequent application to extend the indication to the use of rosiglitazone as monotherapy an integrated dataset consisting of 3293 patients treated with RSG monotherapy, including over 1000 patients treated for 2 years was provided.

Adverse events and serious adverse events/deaths:

In the clinical trials there were no deaths with likely relationship to RSG therapy. The rates of withdrawals due to adverse events AEs in Phase III trials were similar for RSG, placebo and comparators and of the usual magnitude for this type of studies. Relative to placebo, the only types of AEs in the RSG population that caused an increased frequency of premature withdrawal from study were anaemia and hypertriglyceridaemia, reported in 0.3% each (including all patients treated with RSG). The only AEs reported for > 5% of patients on RSG monotherapy were upper respiratory tract infection and injury. As expected from the pharmacological mode of action, hypoglycaemia is not an AE of RSG monotherapy and was reported accordingly only in 0.6%. The available experience did not suggest qualitative changes of the AEs profile with prolonged treatment duration up to 18 months. However, the available study results at the end of the initial application were not considered sufficient to assess potential long-term toxicity.

In combination studies, there were no indications of potentiation by RSG of adverse effects associated with SU or metformin or *vice versa*. In addition, according to updated data presented in the appeal documentation the majority of AEs across the combination program were considered to be mild or moderate. Withdrawal due to AEs expressed in rates per 100 patient years decreased compared with the marketing authorisation application (MAA) and the Safety Updates (Table 4).

Table 4: Rate of withdrawals due to AEs per 100 patient years in the MAA and safety update databases

	MAA	**First Safety Update**	**Second Safety Update**
RSG+SU			
Ptyrs*	552	774	1042
rate/100ptyrs	11.0	10.0	8.83
SU			
Ptyrs*	363	542	588
rate/100ptyrs	13.23	11.25	10.71
RSG +MET			
Ptyrs	272	403	646
rate/100ptyrs	14.0	11.09	9.59
MET			
Ptyrs	98		
rate/100ptyrs	13.25		

* ptyrs = patient-years

For other abbreviations see Table 1

The profile of adverse events for RSG monotherapy or in combination with SU or metformin has not changed since the First Safety Update.

A comparison of the data in the appeal documentation with the data in First Safety Update showed small increases in the relative frequency of AEs which may be expected during long-term treatment. Concerning the common AEs and those related to the pharmacology of thiazolidinediones, oedema, anaemia and elevated lipid parameters, a comparison of rates per 100 patient-years with MAA, First Safety Update and Second Safety Update showed that with time the rates decreased. There was no evidence that AEs commonly associated with either SU or metformin were exacerbated when RSG was added. The overall rates of SAEs have not changed since the MAA; the most frequently reported SAEs were cardiovascular. Overall the additional data did not indicate a change in the safety profile and provided reassurance because of the increased treatment duration.

Cardiovascular safety

Cardiovascular safety in relation to RSG in combination with insulin:

Safety data from the ongoing clinical program of RSG in combination with insulin have been submitted in the course of the initial evaluation. The data referred to safety only. In these trials, the combination of RSG plus insulin was associated with a clear trend to increased incidence of congestive heart failure, CHF (RSG+insulin 2.5%, insulin alone 1% RSG+SU:0,6%, RSG+Metformin:0,3%). One possible explanation is that in the insulin add-on trial there were differences in the baseline parameters of the patients as shown in additional post-hoc analysis. Secondly, in order to achieve maximal glycaemic control, patients were given a fixed dose of 8mg RSG without titration and the high dose of insulin was fixed at study entry. Thirdly, patients in the insulin combination studies had a longer disease duration (in the trial a mean of 12.8 years) compared to 8.7 and 7.5 years for the oral combination treatment trials of SU+RSG and metformin+RSG respectively.

Cardiovascular safety in relation to RSG monotherapy and combination with SU or metformin:

In contrast to the increased incidence of CHF observed with the insulin combination, no increased incidence of new-onset CHF compared with placebo was observed with RSG. In the presented target population, there were only isolated cases of worsening of pre-existing CHF during RSG treatment. In addition, RSG was not associated with aggravated hypertension or specific ECG changes. In three echocardiographic studies (12 to 36 months) no clinically relevant effects on left ventricular mass index (LVMI) were observed.

In the appeal documentation the rates of all cardiovascular events (expressed per 100 patient years) with RSG in monotherapy or in combination with SU or metformin were equal to either SU or metformin alone and did not increase between the MAA and the Second Safety Update.

The possibility to assess a large database was considered reassuring:

- with more than 1,000 patients treated with RSG for at least 24 months
- with more than 2,000 patients treated with RSG for at least 12 months
- with more than 3,000 patients treated with RSG for at least 6 months.

Hence, it is concluded that the cardiovascular risk is not increased in the short-term as assessed using this very large database. However, the patients treated in the clinical trials conducted so far were devoid of manifest pre-existing severe CHF (NYHA class III or IV) and insufficient data are presently available to exclude progression in subclinical left ventricular dysfunction in patients with mild or moderate pre-existing cardiac dysfunction.

Fluid retention:

In the preclinical program for RSG cardiac hypertrophy findings in animal models were considered to be due to plasma volume expansion. An increase in plasma volume of approximately 4% relative to placebo was found with 8 mg/d RSG in a Phase I trial in healthy volunteers. In double-blind trials, oedema of mild to moderate intensity was reported with higher frequency in RSG group (4.9%),

compared with placebo and comparator medications. Higher incidences of oedema were seen in the small number of patients with pre-existing CHF studied (20%), and in patients > 75 years old (13%).

No new data were provided in the appeal documentation regarding the pathophysiological mechanism of fluid retention. With longer treatment duration the cumulative incidence of oedema increased in all RSG groups between the First and Second Safety Update although when expressed per 100 patient years the rate of oedema did not increase over time (RSG+SU: MAA 7.42; First Safety Update: 8.0; Second Safety Update: 6.14. RSG+Met: MAA 15.05; First Safety Update;14.40; Second Safety Update: 12.38). In approximately 50% of oedema cases corrective therapy with diuretics was used. There was no change in incidence of CHF with RSG monotherapy or with RSG oral combination therapy between the First and Second Safety Update. Furthermore, the rate of CHF had not increased in the updated monotherapy dataset (February 2003) despite the increased exposure and duration of treatment. These data are reassuring.

In addition, new data were presented showing statistically significantly decrease in diastolic blood pressure with RSG treatment in the total population. The outcome has not been analysed for patients with hypertension.

Considering the signal in the insulin combination, the risk of fluid retention and pending further safety data, it is concluded that RSG treatment is not appropriate in patients with cardiac failure or with a history of cardiac failure. Furthermore, concomitant use of medications, such as NSAIDs, which can cause fluid retention may increase the risk of oedema with RSG.

Effects on red blood cell parameters

Dose-related reductions of Hb and Hct were seen in clinical trials with RSG and were at least partly explained by the induced haemodilution. Anaemia was reported as an AE in 1.9% of patients on RSG monotherapy, increasing to 7.1% among those treated with a combination of RSG and metformin: this is likely to reflect low baseline levels of Hb prior to the addition of RSG. No cases of severe anaemia were reported, but anaemia was a cause for premature withdrawal in 0.1-0.6% of the RSG treatment groups. The average Hb reduction of 1 g/100 ml seen during RSG should not have clinically relevant consequences in patients with a normal blood value when starting RSG treatment, but anaemia was a frequent finding in patients with low Hb at baseline.

According to the data of the MAA and the First and Second Safety Updates, the incidence of anaemia increased in all treatment groups, markedly in the group of RSG added to metformin, but the rate of anaemia per 100 patient years decreased slightly with time in all treatment groups (RSG+SU: MAA 4.53: First Safety Update 3.75; Second Safety Update 3.55. RSG+Met: MAA 19.09: First Safety Update 15.64; Second Safety Update 12.84).

Effects on body weight

RSG was associated with a gain in mean body weight over time due to increased body fat and there may also have been a contribution from fluid retention. Among patients treated with RSG monotherapy for at least 12 months, approximately 35% gained ≥ 5% in body weight and 11% gained ≥10%, compared with baseline. In the appeal documentation a comparison of weight increases during 24 months was presented. Weight gain occurred primarily over the first 6-12 months of therapy with small increases in all groups up to 24 months. Weight gain with RSG does not seem to be more frequent when RSG is added to SU or metformin compared with RSG alone. In mechanistic studies, the weight gain was predominantly shown to be due to increased subcutaneous fat with decreased visceral and hepatic fat.

Subgroup analyses performed in the different weight gain quartiles of changes in blood pressure, heart structure and function (LVMI, LVEF, LVEDV), lipid pattern and HbA1c concentrations did not reveal any differences across all weight quartiles or in comparison to the other treatments over a period of 12 months.

Effects on lipids

Lipid parameters were secondary efficacy endpoints. The mechanisms of the induced multiple changes in the lipid profile are not known. The magnitude of the increase of the TC and LDLc was 10-15% compared to baseline values after six months of treatment and showed a decreasing trend towards baseline thereafter. The early increase in LDLc is accompanied by a more sustained increase of HDLc

of the same order of magnitude. However the increase in HDLc is not accompanied by the expected increase of Apo A1 concentrations, which cannot be explained with the existing data. Overall, although the ratio TC/HDLc does not change or even decreases slightly, the potential long- term effects of these lipid profile changes are not possible to predict and remain a concern without additional long-term clinical data to provide reassurance. Concerns were also expressed regarding the necessity to introduce statins to manage the changes in the lipid profiles.

Hepatic effects

In preclinical studies gross hepatotoxicity was not observed but increases in liver enzymes were seen in the dog, and hepatic hypertrophy in several species. Adequate monitoring of liver function in the RSG trials submitted in the initial application did not reveal any abnormalities of liver function with likely relationship to RSG treatment. Overall, one patient was prematurely withdrawn due to abnormal liver function tests and in the safety update population treatment was discontinued in one patient, subsequent to the diagnosis of a primary liver cell carcinoma. In monotherapy trials, the incidence of AEs related to the liver and biliary system was identical to that found for placebo (0.7%). Specific AEs associated with abnormal liver functional tests (LFTs) were reported in 0.6% with RSG monotherapy, compared with 0.2%, 2.9% and 1.3% for placebo, SU and metformin, respectively. Laboratory analyses did not show an increased incidence of transition of LFTs from normal to levels of clinical concern with RSG, compared with placebo.

Additional data submitted demonstrated that AEs associated with liver abnormalities remained rare in RSG monotherapy or when RSG was added to SU or metformin in the clinical trials as well as in postmarketing experience with RSG. Although in very rare cases fatal outcome due to hepatocellular dysfunction has been reported, a causal relationship has not been demonstrated.

Effects on the reproductive system

Thiazolidinediones including RSG have effects on ovarian production of sex steroids and effects on estrogen and progesterone levels were seen in two animal species, including primates. The clinical experience with RSG in premenopausal females is limited, but did not reveal menstrual disturbances or symptoms/signs of hypoestrogenism.

Safety in special populations

Pregnancy and lactation: In reproductive toxicity studies, there were no effects on the embryo during early gestation but treatment during mid-gestation was associated with foetal death and retarded foetal development. It is not known whether breast-feeding will lead to exposure of the infant to the medicinal product. It is established medical practice to use insulin for treatment of type 2 diabetes during pregnancy and lactation. As a consequence RSG should not be used during pregnancy or breast-feeding. These observations have been recorded in the SPC.

Age: RSG did not result in any increase in frequency of reports in elderly patients (65-75 year group) compared to the < 65 year group, either when given as monotherapy, or in combination. In the RSG monotherapy studies, AEs for which there did appear to be age-related increases in frequency included anaemia and combined oedema. Other events reported more frequently only in patients >75 years included upper respiratory tract infections, diarrhoea, respiratory disorder, chest pain, insomnia, cardiac failure and arrhythmia. No age-related difference in reports of ALT increases or myocardial infarctions were noted.

Gender: In the overall population, the incidence of AEs reported by males and females was similar, although some AEs such as headache, sinusitis and urinary tract infections as well as oedema and anaemia were reported more commonly in females than in males. There was a trend to more reports of weight gain in females. This may reflect the fact that females tend to have greater fat mass than males. One explanation may be that given that the molecular target for PPARγ agonists is expressed in adipose tissue. There was no difference in the frequency of reports relating to increased lipids, and LFT abnormalities. The cardiovascular tolerability profile appeared similar in male and female patients.

Post-Authorisation safety Data

Following the CPMP review of the second PSUR section 4.8 “Undesirable Effects” of the SPC has been amended to include “Rare cases (frequency >1/10000, <1/1000) of congestive heart failure and

pulmonary oedema have been reported in post-marketing experience."In addition a wording amendment has been introduced to the existing statement in section 4.8 of the SPC, for hepatic events and elevated liver enzymes.

Following the CPMP review of the fourth PSUR section 4.8 of the SPC has been amended to include the wording **"**Very rarely cases (frequency < 1/10000) of angioedema and urticaria have been reported in post-marketing experience."

Through a type II variation a warning regarding rapid and excessive weight gain has been added in section 4.4 "Special warnings and special precautions for use". In addition section 4.8 has been amended to reflect rapid and excessive weight gain.

The safety data submitted with the monotherapy variation did not reveal new or unexpected adverse events. Nevertheless, section 4.8 of the SPC has been updated to reflect the adverse events related to the use of rosiglitzone as monotherapy. In addition the presentation of the ADRs in section 4.8 of the SPC has been modified due to the use of a different cut-off (0.2%) for the definition of "excess" in the comparison with placebo or comparator drug.

Discussion on safety

Anaemia, seen with the highest incidences in patients treated with metformin and RSG in combination (7%) and in elderly patients (4%) is thought to result from the observed volume expansion and not from direct effects on blood formation. A warning has been added in the SPC.

The clinical trial and postmarketing data submitted demonstrated that adverse events associated with liver abnormalities remained rare. However, due to potential class effects, the proposed monitoring of liver function and the special warning in the SPC were considered to be a reasonable approach.

The body weight is a safety concern especially due to the fact that a large proportion of type 2 diabetic patients are overweight. The cardiovascular consequences of both obesity and type 2 diabetes are an issue of concern, taking into consideration also the LDLc increase induced by RSG. The long-term magnitude of weight gain or its metabolic implications cannot be assessed based on the submitted data, which were limited to 2 years. However, the weight increase induced by RSG over a two year period did not impair RSG efficacy on blood glucose control. A recommendation to monitor weight has been added in the SPC.

Although an increase in plasma volume has been demonstrated and mild to moderate oedema were reported with higher frequency upon administration of RSG, there is no evidence to suggest an increased cardiovascular morbidity and mortality upon oral administration of RSG alone or in combination with metformin or SU for a duration of up to 2 years. However, in approximately 50% of oedema cases, corrective therapy with diuretics was used and thus it cannot be excluded that diuretic therapy prevented or masked the development of CHF or hypertension.

The potential long-term effects of the observed changes in the lipid profile on the cardiovascular system cannot be predicted and therefore raise concerns.

The overall data indicates that no particular risks in the short-term are expected for patients without chronic heart failure treated with metformin or SU in combination with RSG, but additional studies are required looking at more sensitive functional parameters (e.g. dynamic parameters during rest and exercise) to detect early onset of cardiac injury. Taking into account also the lipid changes induced by RSG, long-term studies are required to evaluate the potential of RSG to affect cardiovascular morbidity and mortality in patients with long-standing diabetes. It is therefore recommended that the applicant undertake adequate clinical trials with cardiovascular safety as primary endpoint to address these issues. In addition, use of RSG in patients with cardiac failure or history of cardiac failure has been contraindicated in the SPC.

5. Overall Conclusion on quality, efficacy, safety and benefit risk assessment

Quality

The pharmaceutical documentation showed that the quality of the product was acceptable. Physicochemical aspects relevant to the clinical performance of the product have been investigated and are controlled in a satisfactory way.

Preclinical pharmacology and toxicology

In the repeated dose toxicity studies, the main findings were in metabolism and the cardiovascular system. Increased fat deposits, anaemia, cardiac hypertrophy and increased plasma volume were observed on all species tested (rat, mouse, dog), while increased body weight was observed in mouse and rat and increase in plasma ALT and ALP only in dog. In the carcinogenicity study rats developed lipomas due to persistent pharmacological overstimulation of adipose tissue.

Efficacy

- In type 2 diabetics failing on monotherapy significant improvements in glycaemic control were observed with the use of RSG in combination with metformin or SU. Effect on glycaemic control is considered a well-validated surrogate for outcome benefits. However, as a combination therapy with metformin or SU, RSG has not been compared to SU+metformin. Such comparison is needed to evaluate the efficacy of the combination of RSG with SU or metformin against the standard combination treatment in these patients. Hence, taking also into consideration the safety concerns, a marketing authorisation could not be granted for the applied indication; "RSG is indicated for use in combination with sulphonylureas or metformin in patients who are not satisfactorily controlled by either agent alone".
- However, among the patients insufficiently controlled on monotherapy with one of the currently approved oral antidiabetics, there is a subgroup of patients for whom the metformin+SU combination is not an option. Currently the available therapy for these patients would be insulin, and insulin therapy is associated with practical problems in elderly patients as well as the risk of hypoglycaemia. During the course of the appeal process specific data were submitted to support the use of RSG in combination with SU in patients who are not satisfactorily controlled upon monotherapy and show gastrointestinal intolerance to metformin. Furthermore, data were submitted to support the use of RSG in combination with metformin in obese patients who are not satisfactorily controlled upon metformin monotherapy. These patients may generally be expected to exhibit marked insulin resistance and would benefit from therapy with an insulin sensitizer. Therefore, the use of RSG can be recommended for these subgroups of patients for whom an unmet medical need is described.
- Based on a subsequent submission (February 2003) of additional monotherapy data, RSG was also recommended for use as second-line monotherapy, particularly in overweight patients, for whom metformin would otherwise be the first alternative.

Safety

The safety database for RSG contains more than 1,000 patients treated for at least two years with RSG. The safety profile of RSG observed in the updated monotherapy dataset was consistent with that previously observed.

Due to potential class effects, and although the available clinical data do not provide a signal for liver toxicity, the proposed monitoring of the liver function in patients receiving RSG and the special warning was considered to be a reasonable approach.

RSG-induced weight gain over 24 months was comparable to weight gain seen in combination with SU or metformin. However, the magnitude of the body weight increase on the long term and possible associated cardiovascular effects cannot be assessed based on the submitted data and must be investigated in long-term studies.

In spite of the observed plasma volume expansion, there is no evidence to suggest increased cardiovascular morbidity and mortality upon oral administration of RSG alone or in combination with metformin or SU for a duration of up to 2 years. However, the patients treated in the clinical trials conducted so far were devoid of manifest pre-existing severe chronic heart failure (NYHA class III or

IV) and insufficient data are presently available to definitely exclude a detrimental cardiac effect in the long term in patients with mild to moderate pre-existing cardiac dysfunction (NYHA class I or II). Although no particular risks in the short term are expected for patients with mild to moderate pre-existing cardiac failure treated with metformin or SU in combination with RSG, the CPMP agreed that additional studies are required looking at more sensitive functional parameters to detect early onset of cardiac injury. Moreover, in view of the lipid changes induced by RSG, long-term studies are required to evaluate the potential of RSG to affect cardiovascular morbidity and mortality in diabetes patients during long-term therapy.

In discussing the timing of studies to address the cardiovascular risk, some CPMP members maintained that these studies should be performed prior to the marketing authorisation. However, the majority of the CPMP considered that, as the indication for RSG has been restricted to patients with an unmet medical need, these studies could be undertaken as a post-marketing commitment. The applicant has committed to perform the following post-marketing studies to address all open safety issues.

- A double blind study of the effect of RSG on cardiovascular structure and function in type 2 diabetic patients with chronic heart failure NYHA stages I-II.
- A long-term cardiovascular morbidity/mortality study in patients on RSG in combination with SU or metformin.

Benefit/risk assessment

Based on the CPMP review of data on efficacy and safety, the CPMP considered that the benefit/risk profile for rosiglitazone was favourable in the following therapeutic indications:

"as oral monotherapy treatment of type 2 diabetes mellitus particularly in overweight patients inadequately controlled by diet and exercise and for whom metformin is inappropriate because of contraindications or intolerance.

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

- in combination with metformin particularly in overweight patients.
- in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated."