SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Avandamet. For information on changes after approval please refer to module 8.

1. Introduction

Type 2 diabetes (T2D) is a chronic progressive disease characterised by hyperglycaemia. The mechanism responsible for impaired glucose homeostasis is a combination of decreased insulin secretion from pancreatic β cells and insulin resistance resulting in increased hepatic glucose production and decreased glucose uptake in muscle, adipose tissue and liver. Although there is increased insulin secretion in an attempt to compensate for insulin resistance early in the disease, with resultant hyperinsulinaemia, this is inadequate to maintain normal glucose levels and diabetes develops. The aetiology of the disease is complex including both genetic and environmental factors. The commonest factors are obesity and physical inactivity.

The current management of T2D should be directed at both the treatment and prevention of complications including tackling the underlying pathophysiology of the disease. The progressive nature of diabetes is characterised by rises in HbA1c as glycaemic control deteriorates over time (UKPDS 1995). This makes its management difficult with a need to intensify treatment and monitor frequently (UKPDS 33; UKPDS 34). Although the cornerstone of diabetic therapy is diet and exercise, the UKPDS highlighted that only 23% of patients on diet attained HbA1c of <7% at 3 years and this was less than 10% at the end of the study (10 years). Thus to maintain glycaemic control as the disease progresses, there is a need for antihyperglycaemic agents and these are often required in combination. In addition to management of hyperglycaemia to prevent microvascular complications, prevention of macrovascular complications should be considered by aggressive treatment of cardiovascular risk factors associated with diabetes such as blood pressure, dyslipidaemia and central obesity. Metformin is now being recognised as the "gold" standard therapy in T2D patients who are overweight. This follows the results of the UKPDS which showed that patients assigned to metformin had significantly lower risk of death, myocardial infarction and stroke compared with patients who received conventional therapy (diet and exercise).

Sulphonylureas promote insulin secretion. The UKPDS demonstrated that SUs reduced HbA1c and microvascular complications but had no effect on macrovascular complications.

Although the UKPDS highlighted the benefits of metformin and SU therapy it also demonstrated the lack of durability of effect associated with these older agents. By 3 years, less that 55% of patients allocated to any single pharmacological treatment could maintain fasting plasma glucose (FPG) levels < 7.8 mmol/L or HbA1c levels < 7.0%. By 9 years this figure had declined to approximately 25%.

Other additional hypoglycaemic agents less commonly used include the meglitinides and Acarbose. The meglitinides reduce blood glucose by stimulating insulin secretion. Repaglanide (a meglitinide) was designed to normalise post prandial glucose fluctuations and gained approval in the EU in 1998. It is indicated as monotherapy and in combination with metformin (Repaglinide SmPC 1998). Acarbose is a competitive inhibitor of intestinal alpha glucosidases (Acarbose SmPC 1999-2002). It has limited usage and limited compliance due to GI side effects.

Thiazolidinediones (TZD) act by reducing insulin resistance, and have been shown to provide added benefits in terms of reduction in HbA1c when added to either metformin or SU's.

Insulin is clearly an option for the management of T2D but is generally used once control is no longer achieved with a combination of oral agents.

All available data demonstrate the need for polypharmacy in the majority of patients with T2D in order to achieve target glycaemic control. Non-compliance is a major healthcare problem in all therapeutic areas with estimates of non-compliance ranging from 30-60%. An evaluation of the Medicaid patient population with T2D indicates that compliance with SU or metformin monotherapy is 36% higher than that associated with SU or metformin dual therapy (Daily 2001). Compliance can be promoted by the use of a single dosage unit combining two different classes of antihyperglycaemic agents (i.e. a FDC). That is the reason for the development of this FDC of rosiglitazone and metformin.

Avandamet is a fixed dose combination of rosiglitazone and metformin. The proposed indication is "in the treatment of type 2 diabetes mellitus patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone".

Rosiglitazone is a selective agonist at the PPARγ nuclear receptor and reduces glucose by reducing insulin resistance at adipose tissue, skeletal muscle and liver. In animal models rosiglitazone preserved pancreatic islet mass and insulin content and prevented the development of overt hyperglycaemia. The glucose lowering effects in clinical trials was gradual in onset with near maximal reductions in FPG following approximately 8 weeks of treatment.
Metformin is a biguanide that has antihyperglycaemic effects. The main mode of action of biguanides includes a reduction in hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis. Other effects delay intestinal glucose absorption and increase insulin sensitivity and glucose uptake into cells, particularly muscle. Metformin stimulates intracellular glycogen synthesis and increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4). Clinical studies have demonstrated a favourable effect on lipid metabolism independent of its glucose lowering effect.

This is a stand alone application for a Marketing Authorisation (MA) according to Council Regulation EC No. 2309/93 (a centralised procedure).

For the rosiglitazone component, reference is made to the original rosiglitazone application Avandia EU/1/00/137/001-012, approved in the EU in 2000. For metformin a bibliographic review is presented to provide justification for metformin's 'well established use'. Two oral strengths are proposed containing 1 mg rosiglitazone and 500 mg metformin hydrochloride or 2 mg rosiglitazone and 500 mg metformin hydrochloride(1/500 mg or 2/500 mg tablets).
Concerning the chemical-pharmaceutical information, in several sections also reference is made to the information already provided for Avandia.

2. Chemical, pharmaceutical and biological aspects

Composition

Avandamet is a fixed dose combination of rosiglitazone and metformin hydrochloride. Two oral strengths are proposed containing 1 mg and 2 mg rosiglitazone (as free base) corresponding to 1.33 mg and 2.65 mg respectively to rosiglitazone maleate combined with metformin hydrochloride. They are presented as film coated tablets

Apart from this difference in strength, the two formulations are identical, excipients include in the tablet core: sodium starch glycollate hypromellose, microcrystalline cellulose, lactose monohydrate, povidone, magnesium stearate ,and in the film coat: hypromellose, titanium dioxide, macrogol 400, iron oxide yellow /red

Film coated tablets are supplied in PVC/PVdC/aluminium blisters.

Active substance

Two drug substances are used in this fixed combination product, rosiglitazone maleate and metformin hydrochloride.

Rosiglitazone maleate

The route of synthesis, site of manufacture, and control of rosiglitazone maleate drug substance are the same as accepted earlier in an authorisation for rosiglitazone tablets, (Avandia).

As before, the tests and limits in the specifications are considered appropriates for controlling the quality of this active substance,

The stability studies concern the same studies and batches for which results already were provided for the commercial rosiglitazone tablets (Avandia). For this application however results are presented now covering 36 months at 25ºC/60% RH for 4 qualification batches and for 3 production scale batches (validation batches) and accelerated conditions (40ºC/75% RH) for 6 months for 4 validation batches and 12 months for 3 qualification batches.

As before, the stability results for rosiglitazone show no evidence of degradation when compared to the initial time point. There were no significant difference in assay content, related substances profile or water content results. The infrared spectrum showed no evidence for change in crystalline form or level of hydration.

The results of the photostability study were conducted in line with the ICH guideline for photostability testing, indicate that there is no necessity to take unusual precautions to protect the substance from light.

The re-test period proposed is acceptable according to the stability data submitted.

Metformin hydrochloride

Information on metformin hydrochloride has been supplied in the form of an EDMF.

Adequate In-Process Controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents, have been presented.

Metformin hydrochloride specifications include tests for description, identification (IR, melting point, chlorides test), melting point, chlorides test, assay (HPLC), related substances(HPLC) residual solvents(GC), particle size, heavy metals(Ph Eur), sulphated ash(Ph Eur), loss on drying(Ph Eur), solubility(Ph Eur)
Batch analysis data of the three lots of metformin hydrochloride drug substances are provided. The three lots are within the specifications and consistent from batch to batch.
The tests and limits in the specifications are considered appropriate for controlling the quality of metformin hydrochloride.
According to the literature, Metformin hydrochloride is very stable in the solid state. It thermally decomposes only at temperature exceeding 230°C. However, on exposure to alkaline solutions it decomposes to form ammonia and dimethylamine. Forced degradations studies have been performed in order to confirm the literature data.
The long term storage conditions were used according FDA guideline until February 2000 (i.e. 25 – 30°C and ambient humidity) and ICH guidelines since February 2000 (i.e. 25°C / 60%RH) in 10 batches during up to 60 months.

The parameters tested were: description, solubility, melting point, loss on drying, assay and related substances.
One batch of drug substance was also exposed to light in line with ICH guideline for photostability testing.

In view of these results and the information from literature, the proposed re-test is acceptable.

Other ingredients

The excipients sodium starch glycollate hypromellose, microcrystalline cellulose, lactose monohydrate, magnesium stearate, Povidone are tested according to PhEur.

The iron oxide yellow and red meet the requirements of E172 in EC Directive 95/45/EC.

Regarding the TSE compliance of the excipients, the lactose monohydrate is classified as a category IV excipient in the CPMP Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

Tablets are packed into blister strips. The blister strip comprises an opaque white PVC film with a PVdC layer, sealed with an aluminium lidding foil with a vinyl acrylic heat seal coating. The packaging components comply with directives pertaining to suitability for direct contact with foodstuffs.

Product development and finished product

As the product is a combination of two existing oral antidiabetics, the product was developed to be bioequivalent to commercial products containing the individual active substances. The tablet formulations were developed to provide fast release of both active substances, and to incorporate the same, stable, granular concentrate of rosiglitazone maleate than those were established for the manufacture of commercial rosiglitazone tablets.

The tablet formulations used during the clinical trials were identical to those of the proposed commercial formulations.

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During formulation development, the particle size distribution of the two active substances, and the compatibility of the active substances with the excipients in the proposed formulation was examined. No major incompatibility was found.

The manufacturing process is comprised of several steps: the active substances are mixed together with the excipients, and the obtained mass is compressed into tablets.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process in three production-scale batches of each and is satisfactory**.** The in process controls are adequate for this film coated tablet preparation.
The batch analysis data show that the film coated tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product Specification
The product specifications include tests by validated methods for description, identification of metformin hydrochloride (HPLC), identification of rosiglitazone maleate (HPLC), assay of the active substances (HPLC), uniformity of dosage units (Ph Eur), dissolution profile, microbiological purity (Ph. Eur).
Batch analysis data on three production-scale batches (validation batches) for each of three tablets strengths confirm satisfactory uniformity in the product at release.

Stability of the Product

Stability data of three batches of both strengths stored for 18 months at 25ºC/60%RH and for up to 6 months at 40ºC/75%RH are provided. The batches of tablets are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for description, identification of metformin (HPLC), identification of rosiglitazone maleate (HPLC), assay of the active substances (HPLC), related degradation products, dissolution, identification of the colorants, microbiological purity (Ph Eur), mean hardness, and moisture content.
In addition, samples previously stored at 25ºC/60%RH for 3 months were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.
Based on available stability data, the proposed shelf-life and storage conditions as stated in the SPC are acceptable.

Bioequivalence

An bioavailability and bioequivalence study was performed in order to demonstrate the dose proportionality of the formulation and the bioequivalence of the combination formulation to commercial rosiglitazone and commercial metformin hydrochloride tablets. See clinical part of the report for details.

3. Toxico-pharmacological aspects

The pharmacology of rosiglitazone and metformin has been investigated for both drugs when administered as individual drugs alone. Studies have been performed using a variety of animal species. Reports and summary information previously submitted and reviewed as part of the MAA submitted for each of these drugs individually have been also used.

- *In vitro* **studies**

In vitro data indicate that rosiglitazone activates the peroxisome proliferator activated receptor-gamma (PPARγ) nuclear receptor, which results in increased expression of a number of genes that play a key role in the regulation of glucose and lipid homeostasis. It increases insulin binding, increases insulin-stimulated glucose transport, increases the total adipocyte content of GLUT-4 glucose transporter. Rosiglitazone did not affect phosphotyrosine phosphatase (PTPase), insulin receptor tyrosine kinase (IRTK) or amylin activity.

- *In vivo* **studies**

A number of *in vivo* studies in mouse and rat models of diabetes clearly show that rosiglitazone is a potent and orally active insulin sensitiser with marked antihyperglycaemic activity mediated by improvements in insulin resistance. There is also evidence that early intervention in the diabetic animals can reduce the progress of diabetes induced organ damage.
Both in a mouse and in a rat model of type I diabetes rosiglitazone fails to affect glucose values which illustrates the need of an adequate pancreatic ß-cell reserve for the effectiveness of this drug.

The glucose lowering effect of metformin has been studied in streptozotocin induced diabetic mice, obese hyperglycaemic rats and mice, alloxan induced diabetic rats, genetically diabetic mice, and normal mice, rats and guinea-pigs.

- **Pharmacodynamic drug interactions**

In 1-month rat studies rosiglitazone was combined with the sulphonylurea glibenclamide or with the alpha-glucosidase inhibitor voglibose or with yeast-derived human insulin (Novolin-R). Rosiglitazone did not interact with voglibose. As expected in combination with glibenclamide or Novolin-R as compared to rosiglitazone alone an enhanced therapeutic effect was observed. There was no evidence for new or increased toxicities as result of the combinations.

- **General and safety pharmacology programme**

No new non-clinical safety pharmacology studies were conducted using rosiglitazone/metformin fixed dose combination. The safety pharmacology profile has been investigated for both drugs when administered individually.

In the previous assessment of rosiglitazone it was stated that the preclinical concerns in particular regarding cardiotoxicity should be addressed in clinical postmarketing studies. Observed effects of cardiotoxicity but also hepatotoxicity have been recognised and dealt with in the SPC Conclusions regarding the safety of metformin hydrochloride in metformin tablets have been substantiated by the established clinical safety of this compound, which has been used extensively in patients for over 40 years.

- **Summary of salient findings**

Based on results of preclinical studies it can be concluded that rosiglitazone has high affinity to the PPARγ and that rosiglitazone has shown to be a potent and orally active insulin sensitiser with a

marked antihyperglycaemic activity mediated by improvements in insulin resistance. The slow onset of action of the PPARγ agonist rosiglitazone is in line with the theory that the synthesis of the active products such as lipoprotein lipase and GLUT-4 induced by activation of PPARγ-responsive genes needs time. Accordingly, the duration of action and offset time will be determined by the half-life of these products rather than by the binding of rosiglitazone to PPARγ per se.
The results of the newly submitted pharmacodynamic studies do not include clear advantages or disadvantages for the efficacy and safety of rosiglitazone. The contribution of M10 into the efficacy of rosiglitazone remains unresolved.

Metformin is a biguanide with antihyperglycaemic effects and a multifactorial mode of action. The first studies were performed with metformin in the 1950s. The precise mode of action of biguanides remains unclear but possible mechanisms of action include a reduction in hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis, delaying intestinal glucose absorption and modestly increasing insulin sensitivity and glucose uptake into cells, particularly muscle. Metformin stimulates intracellular glycogen synthesis and increases thetransport capacity of certain types of membrane glucose transporters (GLUT-1 and GLUT-4).
Unlike the sulphonylureas, metformin does not act by stimulating additional release of pancreatic insulin. It has no significant effects on the secretion of glucagon, cortisol, growth hormone or somatostatin. Since the first studies were performed with metformin in the 1950s, there has been increasing recognition of the effectiveness of metformin as an antihyperglycaemic agent.
Preclinical studies on the efficacy of the combination of rosiglitazone with metformin were not conducted.

Pharmacokinetics

The applicant focussed on biotransformation and excretion studies of rosigitazone in mice and on the extent of plasma protein binding of metabolite M10. In addition, the applicant carried out a pharmacokinetic study of rosiglitazone in juvenile rat.
The applicant submitted a new method for determination of rosiglitazone in plasma of juvenile rats because smaller aliqouts of plasma needed to be examined compared to the previous method, submitted before for registration of rosiglitazone only.

Absortion

Following oral administration of rosiglitazone maleate, the bioavailability of rosiglitazone was high. Mean absolute bioavailability was found to be approximately 100%, 60% and at least 95% in rat, dog and man, respectively. Rosiglitazone has thus been shown to be well absorbed and does not undergo substantial presystemic elimination in rat, dog and human. Absorption was rapid, T_{max} values generally being 0.5 to 2 hours.
After single oral dosing in the juvenile rats, systemic exposure to rosiglitazone generally increased proportionally with dose, with no apparent sex differences. Similarly in adult rats, systemic exposure was proportional to dose increment up to 2 mg/kg, but subproportional thereafter and generally 50-100% higher in females than in males. Exposure to rosiglitazone was generally lower in male and female juvenile rats, at 20-50% and 12-40% of adult values, respectively.

Oral absorption of metformin in animals is rapid, with peak plasma levels being obtained within 30 minutes in mice, 1 to 2 hours in rats, 1.75 hours in dogs and 0.75 to 2 hours in monkeys.
In man, the absolute bioavailability of metformin varies between 50 and 60% and gastrointestinal absorption is apparently complete within 6 hours of ingestion. This low bioavailability is most likely a result of being protonated at intestinal pH as well as its poor solubility.

Distribution

Rosiglitazone-related material distributes rapidly into the tissues of the albino rat following oral administration of ^{14}C-rosiglitazone maleate. Tissue concentrations were generally lower than the corresponding plasma concentrations, which is consistent with the low volume of distribution observed for the parent drug. In pigmented rats, quantifiable drug-related material was still present in

melanin-containing tissues (uveal tract and pigmented skin) 35 days after dosing. This infers some affinity of rosiglitazone and/or its metabolites for melanin.
The plasma protein binding of rosiglitazone was comparably high (>98%) in the mouse, rat and man, but slightly lower in the dog. Due to the high protein binding of SB-332650, the major human metabolite of rosiglitazone in man (M10), to plasma in man and dog (in excess of 99.9%), it was not technically possible to obtain data even at the highest plasma levels, however it was estimated that the plasma free fraction of SB-332650 was 28-fold lower than that of rosiglitazone in man. Binding of SB-332650 to plasma proteins was comparable in mouse and rat. The assumed higher protein binding of M10 compared to rosiglitazone reduces the contribution of M10 in the blood glucose lowering potential of rosiglitazone.
Drug-related material crosses the placenta of the rat following oral administration of ^{14}C-rosiglitazone maleate and is secreted in the milk of lactating rats.

For Metformine, after a single oral dose in mice, radioactivity first appeared in the stomach, urinary tract and bladder and later in the salivary gland and intestinal walls. The highest radioactivity was found in the kidneys, adrenals, pancreas, liver, lungs and intestinal wall with little localised in brain or fat. Multiple doses showed no apparent accumulation in the tissues. Rats were similar to mice.
At 2 hours following oral administration to pregnant rats on Day 16 of gestation, levels of radioactivity were generally lower in the foetus than in maternal tissues.
Metformin was also demonstrated to cross the placenta in rabbits following oral administration on Day 18 of gestation.
When given to lactating rats, the ratio of total radioactivity in the milk to plasma was generally increased at later time points and had increased significantly by 24 hours post-dose.

Metabolism

Rosiglitazone was extensively metabolised following oral administration in the mouse. The main routes of biotransformation were similar to those previously observed in rat and man.

No metabolites of metformin were found following chromatography of urine, faecal and/or plasma samples from mice, rats, dogs, monkeys or humans. However, one metabolite, N-desmethyl metformin (N-monomethylbiguanide), occurs in the rabbit.

Excretion

Similar to other animal species, rosiglitazone was mainly excreted via the faecal route. In man the urinary route predominates.

After oral administration of 50-mg/kg metformin, excretion in the dog is mainly in the urine, with the monkey excreting almost equal amounts in the urine and faeces by 48 hours. Elimination of metformin into the urine is via tubular secretion.

In short, the submitted additional pharmacokinetic studies generally do not change the current non-clinical view on rosiglitazone except for the fact that the contribution of M10 to the pharmacological effect of rosiglitazone is likely to be reduced substantially.

Toxicology

According to the NfG on fixed-combination products (CPMP/EWP/240/95) non-clinical animal studies with the active substances are needed unless the substances have been extensively (600 patients) and safely used in humans in identical/similar combinations for a long period of time (≥ 6 months). In the strict sense this is not possible for AVANDAMET as rosiglitazone has been granted a marketing authorisation since July 2000. Nevertheless additional non-clinical studies with the combination are considered not necessary since the submitted PSURs for rosiglitazone (PSUR 6, August 2002) did not indicate the need for additional non-clinical studies. In addition, non-clinical data on metformin revealed no special hazard for humans based on conventional toxicity studies. In the previous assessment of rosiglitazone it was stated that the preclinical concerns in particular

regarding cardiotoxicity should be addressed in clinical postmarketing studies. Therefore, additional non-clinical studies are not needed with the fixed combination product.

Administration of single intravenous doses of SB-332650 (human metabolite, M10 of rosiglitazone) to male and female mice at up to 60 mg/kg did not result in any adverse effects. Higher doses were precluded by solubility limitations. The study is partly inconclusive, as effects due to activation of the PPAR receptors are not accounted for. A repeated dose study with M10 might have been more appropriate. Nevertheless, a repeated dose toxicity study with M10 will not be required, as the outcome will not change our current preclinical view on rosiglitazone.
For metformin, rabbits and dogs were more sensitive to the acute effects of the product than mice or rats. Signs of toxicity included decreased activity, ataxia and diarrhoea in all species. Single dose oral studies demonstrated that metformin has a low order of toxicity.

Repeat dose studies of at least 12 months in duration in mice, rats, dogs and monkeys have been performed with metformin. Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.
Observations from the juvenile rat toxicity study with rosiglitazone were consistent with those reported in adult rats, and there were no unique target organs or effects on physical development of juvenile rats.

Other studies performed on rosiglitazone or its metabolites presented did not identify any new safety issues and generally confirmed or investigated known toxicities.

A full package of genetic toxicology and carcinogenicity studies has been performed for each product individually. There were no results in any of these studies that would cause concern over the safety of concomitant administration of rosiglitazone and metformin. Thus no further investigations were needed to support the use of the rsg/met FDC product.

A full range of reproductive toxicity studies was submitted along with the previous rosiglitazone application. The main effects observed, the impaired female fertility and the impaired post natal development were only observed at multiples of clinical exposure and therefore not clinically relevant. Fertility and reproductive performance of male and female rats was unaffected by metformin at doses up to 600 mg/kg/day, which is approximately twice the maximum recommended human daily dose based on body surface area comparisons (Dollery, 1999). No effects of metformin on embryonic development were observed in rats or rabbits at oral doses of up to 600 or 140 mg/kg/day respectively.

An environmental risk assessment (ERA) for rosiglitazone maleate and metformin hydrochloride (derived from use of Avandamet tablets) has been undertaken. This ERA concludes that the compounds derived from Avandamet released into the environment are not expected to have any adverse effects. No adverse environmental effects are expected to occur as a result of emissions associated with the disposal of unused product.

Discussion on toxico-pharmacological aspects

Taking into account the precautionary measures in the SPC with respect to cardiotoxicity and hepatotoxicity, the preclinical information provides good assurance of safety for rosiglitazone for use in rosiglitazone/metformin Fixed Dose Combination tablets at the proposed therapeutic dose for the treatment of diabetes in humans. In addition, the non-clinical data on metformin revealed no special hazard for humans based on conventional toxicity studies

4. Clinical aspects

This application concerns a fixed dose combination (FDC) of rosiglitazone and metformin (rsg/met FDC). Rosiglitazone (Avandia) is a thiazolidinedione that was approved via the central procedure in the EU in 2000 for combination treatment of type 2 diabetes (T2D) in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy. At the time of submission of the

Avandamet Marketing Authorisation Application, Avandia was licence for combination use with metformin in obese patients and consequently the clinical section of the MAA refers to the obese patient group. The Avandia licence has subsequently been amended to allow combination use with metformin particularly in overweight patients and to ensure consistency, the Avandamet indication has been amended accordingly

Clinical pharmacology

In support of the application two new pharmacology studies were submitted. These studies serve to bridge the FDC tablet to the original approval of rosiglitazone and metformin combination therapy in obese patients. These new studies establish the bioequivalence and dose proportionality of the rosiglitazone/metformin fixed dose combination to the concomitantly administered rosiglitazone and metformin.

Pharmacodynamics

- Mechanism of action

Rosiglitazone is a selective agonist at the PPARγ nuclear receptor and reduces glucose by reducing insulin resistance at adipose tissue, skeletal muscle and liver. In animal models rosiglitazone preserved pancreatic islet mass and insulin content and prevented the development of overt hyperglycaemia. The glucose lowering effects in clinical trials was gradual in onset with near maximal reductions in FPG following approximately 8 weeks of treatment.
Metformin is a biguanide that has antihyperglycaemic effects. The main mode of action of biguanides includes a reduction in hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis. Other effects delay intestinal glucose absorption and increase insulin sensitivity and glucose uptake into cells, particularly muscle. Metformin stimulates intracellular glycogen synthesis and increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4). Clinical studies have demonstrated a favourable effect on lipid metabolism independent of its glucose lowering effect.

Dynamic studies:
No studies were submitted in which pharmacodynamics of the FDC were investigated. Pharmacodynamics of both components administered together were sufficiently studied and described in the previous marketing authorisation application.

Pharmacokinetics

- General:

This application was supported by two pharmacokinetic studies, i.e. a bioequivalence/dose proportionality study and a food-interaction study. Furthermore, reference was made to a steady-state pharmacokinetic interaction study between rosiglitazone (Avandia) and metformin, which was already assessed for the application of Avandia.

The pharmacokinetics of rosiglitazone 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, rosiglitazone was rapidly and completely absorbed. Maximum plasma concentrations were reached about 1 hour after dosing at all dose levels.
The pharmacokinetic parameters of rosiglitazone are proportional to dose in the dose range 1 to 8 mg.
The absolute bioavailability was 99%. Based on absorption data rosiglitazone can be taken without regard to food as the rate, but not the extent of absorption was influenced by food. Rosiglitazone 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. Rosiglitazone is almost completely metabolised with no unchanged parent compound excreted in the urine or faeces.
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 rosiglitazone as the protein binding of M10 is very high (>99.99%). Although the bulk of the data indicates that rosiglitazone 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.

Absorption of metformin takes place mainly from the small intestine, with an estimated half-life of 0.9 - 2.6 h. Studies have established that metformin is incompletely absorbed, with faecal recovery being about 30% of an oral dose. The absorption is slower than the elimination, with peak plasma concentrations reached after 2 h or later.
Oral bioavailability of doses between 500-1000 mg is 50-60%. Concomitant food intake may slightly impair metformin absorption; absorption is completed within 6 h.
Once absorbed, the distribution of metformin is rapid, and has linear pharmacokinetic properties. Salivary glands, kidney and liver persistently accumulate metformin more then two-fold above plasma concentrations, while heart and skeletal muscle accrue concentrations above those of plasma at some time intervals. Metformin is not bound to plasma proteins.
Metformin is excreted unmetabolised in the urine in laboratory animals. The same finding was observed in man following early pharmacokinetic studies. But although some metabolic transformation may occur, neither conjugates nor any other metabolites of metformin have been identified.
Estimates for the mean plasma elimination half-life ranges from 1.5-6.5 h. It is prolonged in patients with renal impairment and is correlated to creatinine clearance. Therefore, there may be some prolongation of the half-life in the elderly because of deteriorating renal function. Appropriate advice on the use of metformin in the elderly population is presented in the metformin EU harmonised SPC.
There are no human data on excretion in breast milk, but studies in lactating rats show excretion of metformin into milk. There is no placental transfer of metformin.

- Interaction studies:

There is surprisingly little literature available on the potential interactions of metformin and alcohol. However, the potential for interaction is recognised as clinically important. The interaction of alcohol and metformin potentates the antihyperglycemic and hyperlactatemic effect of metformin by inhibiting gluconeogenesis. Hence, patients treated with metformin should avoid alcohol. Acute alcohol intoxication and alcoholism are contraindicated in the SPC, which advises to "avoid alcohol or alcohol containing medications".
Metformin, and therefore Avandament should be stopped prior to or at the time of X-ray examinations with iodinated contrast materials such as intravenous urography and aortography, where a risk exists for temporary renal insufficiency. This is stated in the SPC (Section 4.3 and 4.4)
Glucocorticoids (systemic and local routes), beta 2 agonists, and diuretics have intrinsic hyperglycaemic activity and therefore should be used with caution when taking metformin, and therefore Avandament.
Certain drugs tend to produce hyperglycaemia. These drugs include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered with metformin, the patient should be closely observed to maintain adequate glycaemic control.

The extent of absorption of rosiglitazone is not significantly affected by food. For the rsg/met FDC 4 mg/500 mg tablet, administered under fasted and fed conditions, the 90% confidence intervals for rosiglitazone AUC_{inf} were within the bioequivalence acceptance range of 0.80-1.25. However, the rosiglitazone C_{max} levels are statistically significant reduced under fed conditions, by approximately 22%, compared to fasting conditions. Rosiglitazone $t_{1/2}$ values were similar (approximately 3.50 hours) under fed or fasting conditions.
The effect of food on the rosiglitazone C_{max} and t_{max} in the rsg/met FDC tablet is comparable to the food effect that has been reported for Avandia.

Also for metformin, the extent of absorption is not significantly affected by food, but the rate of metformin absorption is statistically significant reduced under fed conditions, by approximately 15%. This is somewhat less than reported for metformin, where a decrease of approximately 40% under fed conditions is mentioned in the SmPC. The reported differences, however, are not considered clinically significant.
Moreover, also under fed conditions, the rsg/met FDC tablet or the concomitantly administered rosiglitazone (Avandia) and metformin tablets are bioequivalent with respect to the rate and extent of absorption of both rosiglitazone and metformin.
The food-interaction study has been performed with the 4 mg/500 mg strength only. This is considered acceptable, since the rsg/met FDC 1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg tablets are dose-proportional with respect to rosiglitazone.

Co-administration of rosiglitazone and metformin does not influence the steady-state pharmacokinetics of either drug, compared to either drug administered alone.

- Bioequivalence studies:

The 4 mg/500 mg rosiglitazone/metformin fixed dose combination (rsg/met FDC) test tablet and the 4 mg rosiglitazone (Avandia) reference tablet were shown to be bioequivalent with respect to the rate and extent of absorption of rosiglitazone, and the 4 mg/500 mg FDC test tablet and 500 mg metformin reference tablet are also bioequivalent with respect to the rate and extent of absorption of metformin.

The pharmacokinetics of rosiglitazone from the rsg/met FDC tablet appears to be dose linear in the 1 mg to 4 mg dose range. This is in line with information on rosiglitazone from the Avandia tablets, for which dose-linearity has been demonstrated in the range 0.2-20 mg. After dose-correction, the 1 mg/500 mg FCD tablet is bioequivalent with respect to the rate and extent of rosiglitazone absorption with both the 4 mg/500 mg FDC tablet and the 4 mg rosiglitazone Avandia reference tablet. The 1 mg/500 mg, 2 mg/500 mg and 4 mg/500 mg FDC tablets are dose proportional, i.e. the only difference is the amount of rosiglitazone granular concentrate. Therefore, also the 2 mg/500 mg FDC tablet, for which no studies were submitted, can be considered bioequivalent with respect to the extent and rate of absorption of rosiglitazone.

Clinical efficacy

Dose-response studies and main clinical studies

Efficacy and safety data relevant to the rsg/met FDC come from three double-blind studies of rosiglitazone in combination with metformin, two of which were included in the original rosiglitazone MAA (093, 094). One study (044) has completed since the MAA. All 3 studies are submitted in this application. Pooled data from these 3 studies (093, 094, 044) has been evaluated in the overall population, and a sub-set analysis is available in the target population of obese patients.

All studies were undertaken in accordance with standard operating procedures of the GlaxoSmithKline Group of Companies, which comply with the principles of Good Clinical Practice. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Where regulatory approval was required, this was obtained from the relevant health authority.

Dose response studies

For the FDC maximum dose of metformin is 2g daily, given in two times. This differs from the dose administered in the clinical studies (2.5g). It is suggested that there will be little clinical benefit from increasing the dose above 2g daily. The Applicant refers to a paper by Garber et al., who observed a maximum efficacy at 2000mg and not 2500mg metformin. However, the explanation for this finding was elusive: it is conceivable that the slightly higher discontinuation rate at the highest dosage may have diluted the effect on glucose variables at the highest dose. There are no formal dose-response studies conducted with metformin. The best studies are that by Garber (1997) and the UKPDS 34, but

also from these studies there is no hard proof that metformin 2g daily is the optimal dose. However, the overall impression is that increasing the metformin dose above 2000 mg adds little to the efficacy whereas there is a clear increase in gastro-intestinal side effects. The UKPDS used a twice-daily regimen, and from that study it can be concluded that this regimen is effective.

Main studies (phase III = therapeutic confirmatory trials)
The efficacy data for Rosiglitazone and metformin are public available and will not be repeated in this report. The evaluation will focus on the new submitted data: Study 044 and the pooling of this new study with the existing ones 093 and 094 to evaluate the target population of obese T2D.

1. Description of the study
Both studies 093 and 094 were randomised, double-blind, placebo-controlled trials in patients who were not adequately controlled on maximal metformin monotherapy (i.e. 2.5 g daily). In study 094 the effects of two different doses of RSG (4 mg and 8 mg od) added to metformin were compared to metformin monotherapy. Metformin was given as open treatment (2.5 g daily) in 500mg tablets to be taken in 2-3 times daily. In study 093 the effects of RSG 4 mg bd + metformin were compared to those of each agent alone. Metformin (2.5 g daily, 250 mg tablets) had to be taken 3 times a day: 4 x 250 mg in the morning, 2 x 250 mg in the afternoon, and 4 x 250 mg in the evening.

Study 044, conducted more recently, was a randomised, double-blind, multicenter, placebo-controlled study with duration of 26 weeks. This study evaluated the effects of metformin alone or metformin and rosiglitazone 2 mg or 4 mg bid on HbA1c and FPG levels in Mexican Americans who were inadequately controlled on 2.5 g a day metformin.
Study participants were type 2 diabetic patients inadequately controlled on a daily dose of 2.5 g metformin. Numbers of patients included in study 093, 094 and 044 were 306, 339 and 152, respectively.

Study 044 was conducted in 5 centres in Mexico and 5 centres in Canada. Inclusion criteria were: males and females, 40 to 80 years of age, with a diagnosis of type 2 diabetes mellitus; patients with fasting C-peptide ≥0.8ng/mL at screening and with FPG ≥140mg/dL and ≤300mg/dL at the visits 2 and 3 of the four week metformin maintenance period (2.5g/day). Exclusions included clinically significant renal or hepatic disease, anaemia, severe cardiac disease, evidence of left ventricular hypertrophy, and hypertension (if systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg). Patients were randomised either to rosiglitazone administered 2mg or 4mg twice daily or to placebo in a ratio of 1:1:1. The randomisation list was computer generated with a fixed block size.

A total of 237 patients who completed study 093 and 290 patients who completed study 094 were eligible to participate in the open-label extension study 113. Of these patients, a total of 460 (201 or 85% of patients who completed study 093 and 259 or 89% of patients who completed study 094) were enrolled into this study.

2. Primary endpoints
In study 044, the primary objective was to evaluate the efficacy of rosiglitazone in reducing hyperglycaemia when added to the therapy of NIDDM patients who were inadequately controlled on a maintenance dose (2.5g/day) of metformin. The primary endpoint was the reduction from baseline in HbA1c after 26 weeks of treatment in the rosiglitazone/metformin combination groups (rosiglitazone 2mg bid or 4mg bid plus metformin 2.5g/day) in comparison with the metformin monotherapy group (rosiglitazone placebo plus metformin 2.5g/day).
The secondary objectives were 1) To compare the change from baseline (visit 4) in the metformin monotherapy group with the rosiglitazone/metformin combination groups in fasting plasma glucose (FPG), fructosamine, C-peptide, immunoreactive insulin, and lipids, including total cholesterol, HDL-cholesterol, LDL-cholesterol (calculated), VLDL-cholesterol, triglycerides and free fatty acids at week 26 (visit 9); 2) To compare two types of responder rates in each treatment group: one with respect to HbA1c (i.e., proportion of patients demonstrating a reduction from baseline of ≥0.7% at week 26), and the other with respect to FPG (i.e., proportion of patients demonstrating a reduction from baseline of ≥30mg/dL at week 26). In addition, the proportion of patients in each group who achieved target FPG

(<140mg/dL) is described; 3) To define the clinical safety and tolerability of the monotherapy and combination groups by the assessment of changes in physical examinations, vital signs, body weight, clinical laboratory tests, adverse experiences and electrocardiograms (ECGs).

3. Statistical analysis

For the assessment of differences between the treatment groups with regard to continuous efficacy variables, an analysis of covariance (ANCOVA) procedure that accounts for the variability due to centres, treatments and baseline was employed. For primary and secondary efficacy variable evaluation, pairwise comparisons for the difference in treatment means (RSG 2 mg or 4 mg bd groups vs. placebo group) were performed using Dunnett's adjustment for two comparisons. Intent-to-treat (ITT) population, which consisted of all randomised patients who had at least one on-therapy data value for an efficacy parameter, was used for efficacy analyses. Each analysis was carried out separately with and without last observation carried forward (LOCF).

RESULTS

4 Study populations/accountability of patients

The demographic characteristics for the intent-to-treat (ITT) population were similar in the three treatment groups except that in the RSG 4mg bd group, more patients were ≥65 years of age and more were female than in the other two treatment groups.

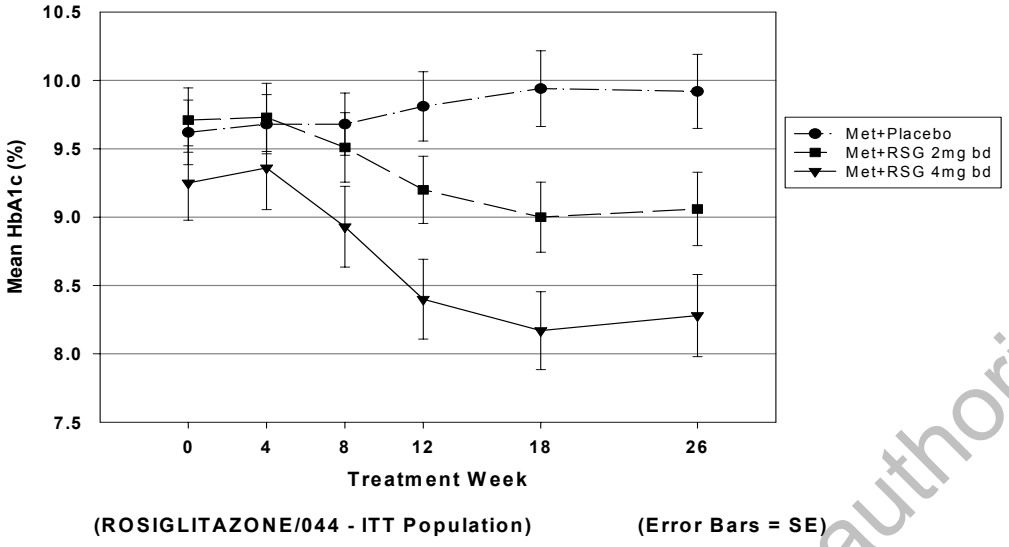
The history of type 2 diabetes mellitus was similar across all treatment groups in the ITT population. Mean baseline HbA1c and FPG were lower in the RSG 4mg bd group than in the other two treatment groups. Few patients in each treatment group (≤6.4%) had been previously treated with diet only. Slightly more patients in each treatment group had been previously treated with a single antidiabetic agent than with combination therapy.

Of the 224 patients who entered the placebo maintenance period, 72 patients withdrew from the study prior to randomisation. Of these, 83.3% did not meet inclusion/exclusion criteria. Overall withdrawal from the study was higher in the placebo group than in either rosiglitazone treatment group

5 Efficacy results

RSG 2mg bd or 4mg bd in combination with a maintenance dose of metformin was effective and well tolerated in patients with NIDDM previously inadequately controlled on metformin alone. Significant decreases in HbA1c were showed in both RSG groups. Fructosamine and C-peptide showed significant decreases compared to placebo. Significant differences in the proportion of HbA1c responders and FPG responders were reported in both RSG groups. The responders analysis showed a statistically significant difference in the number of HbA1c responders in the rosiglitazone treatment groups compared to the placebo group. Target FPG was achieved in 27% of patients in the RSG 2mg bid and 51% of patients in the RSG 4mg bid group compared to 9% in the placebo group.

Mean HbA1c decreased from week 0 to week 18 in both RSG treatment groups and then appeared to plateau to week 26. Mean HbA1c increased slightly in the placebo group between baseline and week 26.



Clinical studies in special populations

No adittional clinical studies were performed for this application

Exploratory analysis performed across trials (pooled analyses and meta-analysis).
The results of study 044 are similar to study 093 and 094 with statistically significant decreases in HbA1c and FPG compared to baseline and to metformin after 26 weeks. In view of the similar designs and results of the double blind studies (093, 094 and 044) data has been pooled and evaluated together. All three double-blind studies (044, 093, 094) individually demonstrated clinically and statistically significant decreases in HbA1c and FPG compared to baseline and to metformin at 26 weeks. The proportion of responders, defined as those achieving a reduction in HbA1c of ≥0.7%, was also statistically greater in patients treated with concomitant metformin and rosiglitazone compared to metformin alone.

Discussion on clinical efficacy
The newly submitted study 044 confirms the results of the formerly submitted studies 093 and 094. There are no formal dose-response studies conducted with metformin. In all the studies the dose of RSG was 4mg or 8mg daily, and metformin was administered in a dose of 2.5g daily mostly in three times. No clinical efficacy studies were performed with the FDC tablet. As the FDC tablet is bioequivalent to both monocomponents, no new clinical studies are necessary. However, there is a difference in dosing. For the FDC maximum dose of metformin is 2g daily, given in two times. This differs from the dose administered in the clinical studies (2.5g). From the number of studies from the literature submitted, it is suggested that there will be little clinical benefit from increasing the dose above 2g daily.
Therefore, in spite of these remarks, it can be concluded that the efficacy of the proposed dosage regime of this combination product has been demonstrated sufficiently.

Clinical safety

There have been no specific safety studies conducted with rsg/met FDC. Limited data are available with the FDC in healthy volunteers from clinical pharmacology studies. The safety profile of rosiglitazone given together with metformin has been presented in the rosiglitazone MAA and the safety profile of metformin has been well established. Seven Periodic Safety Update Reports have been prepared and submitted since the rosiglitazone MAA was granted. No new safety issues have been arisen during this time.

The short term safety of rosiglitazone in combination with metformin has been established in 3 double-blind studies (093, 094, 044). Study 113, an OLE of 093, 094, provides the long-term safety database for rosiglitazone and utilised 8 mg/day rosiglitazone and 2.5 g/day metformin. The result of this study is therefore highly relevant to this application.

Patient exposure

There were 651 patients exposed to concomitant rosiglitazone and metformin during the double-blind and long term OLE study, giving a total exposure of 982 patient years of which 308 were obese (BMI > 30kg/m^2). The results of the obese subset of patients are directly applicable to the proposed target patient population and discussion will concentrate on this subgroup. The safety profile of these obese patients treated with rosiglitazone and metformin is however consistent with that observed in the overall patient population.

Adverse events and serious adverse event/deaths

Adverse events were considered in those studies where rosiglitazone was added to metformin in patients failing maximum doses of metformin (093, 094, 044, 113). In double-blind studies (093, 094, 044), the overall incidence of AEs was higher in the rosiglitazone plus metformin group compared to metformin alone (80.9% vs 72.9%). This higher incidence would be expected given the addition of a new agent. The most frequently reported AEs in obese patients during this period were upper respiratory tract infection (16.5%), diarrhoea (11.7%), anaemia (8.5%), and injury (8.0%).

For obese patients during double-blind and OLE studies, adverse events of particular interest were considered to be hypoglycaemia and those covered under Section 4.4 of the SPC for either rosiglitazone or metformin. In double-blind studies, there was a higher incidence of anaemia (8.5% vs. 2.3%), oedema (4.8% vs. 3.8%), hypoglycaemia (2.1% vs. 1.5%) and weight gain (1.6% vs. 0%) in the rosiglitazone plus metformin group than the metformin alone group. There were no cases of congestive heart failure (CHF) reported in either treatment group during the double-blind phase.

In the long term OLE study there was no comparator arm and the exposure to rosiglitazone and metformin was obviously much greater (30 months) than the exposure in the double blind studies (6 months). A higher number of adverse events were observed in this study. This finding is thought to be attributable to two factors:

Firstly, patients previously treated with placebo or 4 mg rosiglitazone were treated with the higher 8 mg/day in the OLE.

Secondly, as expected the increased exposure confers a higher probability of experiencing normal life events and events attributable to the underlying disease. Because of this, presentation of AEs by incidence will be biased against the open label treatment. To correct for this bias, the AE are also presented by rates per 100 patient years of exposure. Thus although there are more events in the open label studies there is no increase in event rate.

There were no serious adverse events or deaths reported in the clinical pharmacology studies. The overall patient population (n=651) is reviewed here as opposed to the obese subset covered in the previous section. Five deaths were reported during the clinical trial programme, of which one (fatal MI) occurred during the double-blind phase (094). None of the deaths were considered to be treatment related.

A total of 14 (3.2%) patients had reported SAEs whilst receiving rosiglitazone and metformin compared to 8 (2.9%) metformin alone. Not unexpectedly this figure rises to 86 patients 13.2% when the open-label extension study is included.

Discontinuation due to adverse events

A total of 19 patients receiving combination therapy withdrew during the double-blind phase compared to 15 on metformin alone. Withdrawals in the rosiglitazone plus metformin group due to AEs of interest have been reviewed. Two patients (0.5%) withdrew due to anaemia, 1 patient (0.2%) withdrew due to congestive heart failure and one patient withdrew due to hepatic events (0.2%). The overall withdrawal rate was very low (<1%). When withdrawals from the open label extension study (113) are considered there were slightly more patient withdrawals due to these AEs compared to the double-blind period, particularly anaemia (1.1%) and oedema (1.1%).

Laboratory findings
Treatment with rosiglitazone has been associated with anaemia and a 3.1% reduction in hematocrit was observed during the double-blind phase of the studies when rosiglitazone and metformin were administered together.
There were no significant elevations of ALT during the double-blind phase and the incidence was very low 0.2% (0.1 per 100 patient years) during the extension phase. In line with the rosiglitazone SPC, monitoring of liver function is recommended. Both anaemia and hepatic impairment are discussed in Section 4.4 of the proposed SPC.
In line with the metformin SPC, monitoring of renal function is recommended. Renal impairment is discussed in Sections 4.2, 4.3 and 4.4 of the proposed SPC.
There were no other notable effects on laboratory parameters.

Safety in special populations
There is limited data for the use of metformin in patients under 18 years. There is no data available for the use of rosiglitazone in children. Therefore, rsg/met FDC should not be used in children. This advice is reflected in the proposed SPC.
A number of precautions and contraindications are listed in Sections 4.3 and 4.4 of the proposed SPC. These reflect what is known about the individual monocomponents, whether used alone or in combination.

Discussion on clinical safety
There are no new or unexpected safety findings reported in this new application. The known side effects of rosiglitazone; anaemia, weight gain and oedema are known adverse events of rosiglitazone mostly due to fluid retention as previously indicated. Additionally GI symptoms are reported due to Metformin.

In three patients Cardiac heart failure was reported (1%) in the long-term study, which didn't raise concern in this patient population.
With the marketing authorisation application, the applicant has made a commitment for cardiac safety studies for Avandia (rosiglitazone). These studies are planned or on-going at this moment.
Seven Periodic Safety Update Reports have been prepared and submitted since the rosiglitazone MAA was granted. No new safety issues have been arisen during this time (PSUR 7, March 2003). The conclusions of this seventh PSUR were as follows: reporting rates on hepatic events remain very rare; the reports on CHF and oedema are in line with the identified risk for fluid retention by RSG determined during the European review of the MAA and are adequately reflected in the approved SPC; regarding anaemia, there is no new information of interest; reports of pancytopaenia and thrombocytopaenia are not considered to create any real signal, but these issues will be kept under observations in upcoming PSURs; continuing monitoring is warranted for pancreatitis and for interactions with warfarin.

5. Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way At the time of the CPMP opinion, there were a number of unresolved quality issues without impact on the clinical efficacy or safety of the product, therefore the applicant made a commitment to resolve these as post-opinion follow-up measures.

Preclinical pharmacology and toxicology

The pharmacology of rosiglitazone and metformin has been investigated for both drugs when administered as individual drugs alone. No preclinical studies of the combination were conducted.

For rosiglitazone, the results of the newly submitted pharmacodynamic studies do not include clear advantages or disadvantages for the efficacy and safety, and corroborate the previous available information.
In the case of metformin, its effectiveness as an antihyperglycaemic agent has been increasingly recognized since the first studies performed in the 1950s.

From the pharmacokinetic point of view, mice and juvenile rats were the most relevant species for preclinical efficacy and safety studies.
Overall, the toxicology programme provided good assurance of safety for rosiglitazone for use in rsg/met FDC tablets at the proposed therapeutic dose for the treatment of diabetes in humans. In addition, the non-clinical data on metformin revealed no special hazard for humans based on conventional toxicity studies. This information has been included in the SPC.

Clinical pharmacology

Bioequivalence between the rosiglitazone/metformin fixed dose combination (rsg/met FDC) tablets and the rosiglitazone and metformin reference tablets has been sufficiently demonstrated. Furthermore, the pharmacokinetics of rosiglitazone from the rsg/met FDC tablet appears to be dose linear in the 1 mg to 4 mg dose range. Therefore, the pharmacokinetic data provided allow bridging of the FDC tablet to the clinical efficacy and safety data for the rosiglitazone and metformin combination that were obtained for the original application for rosiglitazone.

Efficacy

A newly submitted study confirms the results of the previous submitted studies for the rosiglitazone MAA. Although there are no formal dose-response studies conducted with metformin, it can be concluded that the efficacy of the proposed dosage regime of this combination product has been demonstrated sufficiently.

Safety

The safety profile of rosiglitazone given together with metformin was presented in the rosiglitazone Marketing authorization and the safety profile of metformin has been well established. There are no new or unexpected safety findings reported in this new application.

Benefit/risk assessment

Taking into account that clinical efficacy of adding rosiglitazone (4-8 mg) to metformin (2.5g) has sufficiently been demonstrated, and no new or unexpected safety findings have been reported, it can be concluded that the benefit/risk for this product is positive taking into account the restriction of use as included in the SPC (see also EPAR Avandia).

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered that the benefit/risk profile of Avandamet in the treatment of type 2 diabetes mellitus patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone was favourable and therefore recommended the granting of the marketing authorisation.