London 15 November 2005
Product name: **AVANDAMET**
Procedure No: **EMEA/H/C/522/II/17**

SCIENTIFIC DISCUSSION

1. Introduction

AVANDAMET is currently approved for the treatment of type 2 diabetes mellitus patients (T2DM), particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin (MET) alone.

The Marketing Authorisation Holder (MAH) applied in this type II variation for an extension of indication to add a triple oral combination indication for AVANDAMET with a sulphonylurea (SU). The proposed triple therapy indication is based on data from three clinical studies performed in patients inadequately controlled on the dual combination of metformin and SU. This submission also includes data from a further two clinical studies which are relevant to AVANDAMET.

It is noted that Avandia (rosiglitazone) is already approved as triple oral therapy in combination with metformin and a sulphonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

The MAH proposed to update several sections of the Summary of Product Characteristics and Package Leaflet to reflect the new safety information.

The MAH also applied to update section 5.1 of the SPC to reflect 18-month interim data from a long term ongoing trial for rosiglitazone (RSG) to evaluate the long-term effects of RSG on cardiovascular endpoints and glycaemia.

2. Clinical efficacy

2.1. Clinical studies

The proposed triple therapy indication for AVANDAMET is based on three clinical studies. It concerns **studies 134, CV138055, CV138055 OL TCE** . The studies investigated patients inadequately controlled on the dual combination of MET+SU. These patients went on to receive RSG as their third concomitant therapy. Patients included in the triple combination studies generally had a long duration of diabetes and a high proportion were overweight or obese and were thus representative of patients who might be considered eligible for triple therapy.

Of the three clinical trials, study 134 was conducted by GSK, whereas studies CV138055 and CV138055OL TCE were conducted by another company. Data from these three studies were therefore not integrated due to the different data format and coding dictionaries utilised by both companies.

A total of 1202 patients were included in three triple combination therapy studies. This number does not include patients from study CV138055OL TCE, since these are already accounted for in the core double-blind study CV138055. A total of 900 patients were treated with RSG, comprising of 561 patients from Study 134, 181 patients from study CV138055 and a further 158 patients treated in the OL (open label) extension who were previously treated with placebo.

The three triple therapy studies are summarised in Table 1.

Table 1 Triple Therapy Studies

Study Number	Duration	RSG Total Daily Dose (Regimen)	Treatment Groups[1]	Patient Numbers[2]	
134	26 weeks	4mg (bd) 8mg (bd)	RSG+MET+SU MET+SU	837 (826)	
CV138055	24 weeks	4mg (od) - 8mg (bd)	RSG+MET+SU MET+SU	365 (365)	
CV138055 OL TCE	20 weeks	4mg (od) - 8mg (bd)	RSG+MET+SU	313 (313)	

1. Studies 134 and CV138055 were double-blind, placebo-controlled, i.e. placebo was added-on to background SU+MET. In the BMS studies CV138055 and CV138055OL TCE, MET+SU refers to the fixed-dose combination product Glucovance.
2. Indicates all randomised patients, and in brackets intent-to-treat (ITT) population (i.e., all randomised patients who had a baseline and at least one on-therapy efficacy assessment).
3. Abbreviations: RSG = rosiglitazone; MET = metformin; SU = sulphonylurea (including glibenclamide, gliclazide, glipizide and glimepiride); TCE = triple combination extension; OL= open-label; DB = double-blind; bd = twice daily, od = once daily

Study 134 was a 26-week double blind (DB) study in patients with T2DM. Men and women diagnosed with T2DM and aged between 35 and 75 years were eligible. Fasting C-peptide had to be ≥1.0ng/mL. Patients were taking SU+MET for at least 3 months prior to screening. Following titration to protocol-specified doses of SU (maximal labelled glibenclamide, 20mg/day) and MET (maximally effective doses of 2,000mg/day) combination therapy, patients entered a four-week single-blind placebo run-in/maintenance period. At the end of this period, patients inadequately controlled on combination therapy (FPG ≥140mg/dL and ≤ 270mg/dL) were randomised to receive placebo, 4mg/day RSG, or 8mg/day RSG for 26 weeks, in addition to SU+MET. Doses of SU and MET remained at the protocol-specified doses.

Study CV138055 was a 24-week double blind study in patients with T2DM. Men and women diagnosed with T2DM and aged between 20 and 78 years with BMI ≥23 and ≤40kg/m^{2}were eligible. Prior to study entry, patients were taking either MET+SU combination therapy, or monotherapy with SU, MET or a Thiazolidinedione, for at least 8 weeks, at doses specified in the protocol. The lead-in phase was either 2-weeks or 12-weeks of treatment with MET/glyburide 500/2.5 mg tablets depending on prior treatment history. Subjects were titrated, if needed as per protocol during the lead-in phase, to a maximum dose of MET/glyburide 2000/10 mg. Following the lead-in phase, patients who remained inadequately controlled (HbA1c >7.0% and ≤ 10.0%), were randomised to 4mg/day RSG or matching placebo, in addition to continuing open-label MET/Glib at the same dose, for 24 weeks. During the double-blind RSG treatment phase, patients who had HbA1c ≥7.0 % or FPG ≥126mg/dL, had the RSG dose increased to 8mg/day.

Study CV138055OL TCE was a 20-week OLE of Study CV138055. The study was designed to allow patient rescue from the DB treatment phase for lack of glycaemic control and to collect additional safety and efficacy information on triple combination therapy. Patients who either completed the double-blind RSG treatment phase in Study CV138055, or who were discontinued from CV138055 due to lack of glycaemic control, were eligible. All patients maintained their lead-in MET HCl/Glib dose. Patients taking 4mg/day RSG triple combination therapy, with HbA1c ≥7.0% or FPG ≥126mg/dL, had their RSG dose increased to 8mg/day.

Of the above mentioned studies, study 134 was the pivotal study.

The MAH also included new data from the clinical **studies 002 and 284.** The new data on study 002 use AVANDAMET rather than MET and RSG separately and provide the first clinical trial data on the efficacy and safety of AVANDAMET. Study 284 gives additional efficacy and safety data on RSG.
The new efficacy data of **study 002** provide the first-ever data on the efficacy of AVANDAMET

tablets rather than concomitantly dosed MET and RSG, in a comparison to up-titrated MET mono-therapy. The aim of the study was to investigate whether patients inadequately controlled with moderate doses of MET mono-therapy (MET doses of 2,000mg/day) would gain superior glycaemia control when switched to AVANDAMET, when compared to a high dose MET mono-therapy. The 24-week double-blind, randomised, parallel group, dose escalation study started with a single-blind run-in on MET (2,000mg/day) at baseline, which was followed by randomisation to either AVANDAMET (n=279) or high dose MET (n=272). The 279 patients receiving AVANDAMET were administered 4mg/2,000mg per day, while those 272 patients that were randomised to MET mono-therapy received an additional 500mg/day. After 8 weeks, all subjects were up titrated to either AVANDAMET 8mg/2,000mg or MET 3,000mg as far as tolerable to the study subjects.

Study 284 provides new efficacy data for the concomitant use of RSG with a suboptimal dose of MET of 1 gram per day in patients with diabetes type 2 with various backgrounds ranging from naïve to already using suboptimal dosed MET. The Study was a 24 week double blind, double dummy study, conducted to demonstrate that glycaemia control achieved by the addition of RSG (8mg/day) to the sub-maximal dose MET of l,000mg/day is at least non-inferior and better tolerated than up-titration to the maximally effective dose of MET of 2,000mg/day.
At baseline, patients were randomised to receive either RSG concomitantly (n = 382), or MET mono-therapy (n = 384) in addition to open label MET (1,000 mg/day). Those subjects randomised to receive RSG+MET received a daily dose 4 mg RSG + 1,000 mg MET, while those randomised to MET mono-therapy received an additional 500 mg/day blinded MET so that their daily dose was 1,500 mg/day of MET. After eight weeks, the participating patients were up titrated to either a daily dose 8 mg RSG + 1,000 mg MET, or a daily dose 2,000 mg/day MET.

Reference is also made to 18 month glycaemic efficacy data from a sub-study of **study 231 (RECORD)**, which is a CHMP commitment study for Avandia to evaluate the long-term effects of RSG on cardiovascular endpoints and glycaemia. Study 231 gives additional efficacy data on RSG. This study is mentioned again here due to its use of AVANDAMET.

The MAH provided a statement to that "A total of 6 studies were relevant to GSK's Avandamet variation EMEA/H/C/522/ll/17. All of the study reports contained statements relating to GCP. Trials which commenced before the introduction of Directive 2001/20/EC and which included sites outside the community were conducted in accordance with GCP requirements as set out in Annex 1 of Directive 2001/83/EC. Trials which included sites outside the community and were initiated after the introduction of Directive were conducted in accordance with the ethical standards described in 2001/20/EC."

2.2. Methods

Mean change from baseline in HbA1c was the primary efficacy variable.

2.3. Results

2.3.1. Triple Therapy (studies 134, CV138055, CV138055 OL TCE)

Six month efficacy results for HbA1c changes from baseline in trial 134 are given in Table 2.

Table 2 Study 134: Change in HbA1c at Week 26 Compared to Baseline and Placebo (ITT population with LOCF).

	Treatment Group[1]		
HbA1c (%)	PBO	RSG 2mg bd	RSG 4mg bd
N	272	275	277
Baseline (mean ± SD)	8.7 ± 1.28	8.6 ± 1.14	8.7 ± 1.17
Week 26 (mean ± SD)	8.9 ± 1.49	8.2 ± 1.31	7.8 ± 1.24
Change from Baseline (mean ± SD)	0.2 ± 1.04	-0.4 ± 1.05	-0.9 ± 1.15
95% CI	0.1, 0.3	-0.6, -0.3	-1.1, -0.8
p-value *	0.0054	<0.0001	<0.0001
Comparison with PBO (adjusted mean)	—	-0.6	-1.1
95% CI **		-0.8, -0.4	-1.3, -0.9
p-value †		<0.0001	<0.0001

[1] All patients received MET+SU in addition to study medication

N = Those patients who had both a baseline and a week 26 value (using LOCF).
Reference range <6.5%.
* 1. From paired t-test.
** 2. From Dunnett's procedure using standard error from estimate statements within GLM model.
† 3. From comparisons of LS means within GLM model; significance level: 0.0270.
SAS output is presented in Section 14, Table 14.8.1A.
Data Source: Table 13 CSR.

Dual oral therapy of AVANDAMET as a combination of Metformin with rosiglitazone and triple oral therapy as a combination of Metformin + Sulphonylurea with rosiglitazone, appears to have a clinically small but statistically significant effect in obtaining glycaemic control in diabetics Type 2, in particular adipose patients, as was measured on the parameter HbA1c.

The results are accepted by the CHMP to demonstrate that the add on of RSG to schemas consisting of Metformin (MET) and/or sulphonylurea derivates (SU) achieved small but statistically significant clinical improvements such as of the parameter HbAlc.

2.3.2. Studies 002, 284 and 231

Study 002: At the end of the 24-week treatment period, the mean HbAlc decrease from baseline was 0.17% in the high dose MET mono-therapy group (from 7.5 ± 1.0 to 7.4 ± 1.0) and 0.39% (from 7.4 ± 1.0 to 7.1 ± 1.0) in the AVANDAMET group, which is a small benefit and a small difference with the control arm of the study (p=0.001). It is noted that one patient of the AVANDAMET group did not produce data at Week 24 and was excluded so that the AVANDAMET group was sized n=278 at endpoint evaluation. The reported cause of withdrawal was unrelated to study medication.
Study 284: The MAH's data show that the proportion of patients that attained the treatment goal that was set at HbA1c ≤ 7.0% in the group receiving 8mg RSG and 1,000 mg MET was 57.8% (n=186) versus 48.2% (n=151) in the MET group at the end of the 24 week treatment period of the trial. Statistical analysis of data was not provided.
Study 231: A prospectively defined data analysis of glycaemia control at 18 months of treatment has been carried out. It shows that the achieved target of HbAlc < 7% was 31% in the groups receiving a combination of RSG with MET, compared to 39% in the groups receiving MET+SU. According to the MAH these data are clinically significant, and are the first to show that the combination therapy with RSG achieves similar glycaemia control as the combination of MET+SU. However, statistical analysis of data was not provided.

2.4. Conclusion on efficacy

There is small but statistically and clinically significant efficacy on HbA1 when RSG is added to failing MET + SU in a T2DM population dominated by overweight and insulin-resistant patients.

3. Clinical safety

Safety data on Study 231 (RECORD) have not been reported, as safety data had not been prospectively defined at the present 18 months evaluation point.

Data from the other five studies the Marketing Authorisation Holder has put forward are in line with earlier reporting, and continue to show few serious adverse events (SAEs).

In both study 134 and study CV138055, the incidence of SAEs was low in the RSG combination groups and compared favourably with placebo (PBO) control. A similar incidence was reported in the OLE, study CV138055 OL TCE.

For study 002, the proportion of subjects with adverse events leading to withdrawal was lower in the AVANDAMET group than the MET group (4% vs. 8%). The events most commonly leading to withdrawal were gastrointestinal disorders and the overall incidence of gastrointestinal events leading to withdrawal was higher in the MET group than the AVANDAMET group (5% vs. 3%).
For study 284 the incidence of AEs leading to withdrawal was 35 subjects (9.1%) in the MET escalation group versus 24 subjects (6.3%) in the RSG+MET group.

Deaths were very uncommon in the RSG triple combination therapy. In total 2 deaths were reported, one in a group treated with 4 mg RSG and one in the group treated PBO. The investigators considered both cases unrelated to study medication.

3.1. Oedema

In study 134, a 10% incidence of oedema was observed in the group treated with 4mg RSG+MET+SU, which increased to 14% in the higher dosed 8mg RSG+MET+SU treatment group. A lower incidence of oedema of 8% was reported in Study CV138055 in the group treated with 8mg RSG+MET+SU. That lower incidence may reflect titration of RSG from 4mg to 8mg, instead of initiating therapy at a dose of 8mg, as was the case in Study 134. The recommendation of up-titration treatment strategy from the 4mg to 8mg dose of RSG had already been implemented on the SPC.

3.2. Congestive Heart Failure

The CHMP highlights that rosiglitazone treatment in clinical trials and as guided by the current approved SPC, excludes treatment of patients with cardiac failure or a history of cardiac failure.
The incidence of congestive heart failure was low in the reported studies. In the earlier reported study 134 there were 9 cases (PBO+MET+SU [n=1, 0.4%], 4mg RSG+MET+SU [n=5, 1.8%] and 8mg RSG+MET+SU [n=3, 1.1%]). Cases with cardiac failure have already been reported to have had pre-existing cardiovascular disease.
The study CV138055 and CV1380550L TCE showed no SAEs on congestive heart failure.
New data on study 002 also showed no SAEs on congestive heart failure.
New data on study 284 show five patients with cardiovascular SAEs of which one was considered of suspected relationship with study medication by the investigator. However, the SAE was specified as angina pectoris and not congestive heart failure.
The incidence of congestive heart failure in study 231 (RECORD) is not reported, as safety data had not been prospectively defined at the 18 months evaluation point.

3.3. Anaemia (Dilution Anaemia Related to Fluid Retention)

It had been reported that there was one case of anaemia SAE observed in study 134 that was associated with RSG treatment.

3.4 Hypoglycaemia and Hypoglycaemic Symptoms

The issue of hypoglycaemia is reported to be relevant in the evaluation of triple therapy that includes SU. In study 134 one patient in the 4mg RSG+MET+SU group reported a SAE of hypoglycaemia and

two patients in the 8mg RSG+MET+SU group withdrew from the study due to an AE of hypoglycaemia, with reported FPG <50 mg/dL.
In the triple combination trials of Study CV138055 and the OL TCE extension, multiple daily glucose assessments and proactive solicitation of hypoglycaemia symptoms were performed, and may have accounted for the generally higher reporting of hypoglycaemia. A higher incidence of the feeling of hypoglycaemia was reported in the RSG+MET+SU group (52.5%), relative to the MET+SU group (24.5%). Over 90% of these events were not medically defined hypoglycaemia and required no medical intervention. The hypoglycaemia pattern is similar to that in Study 134, with no SAEs reported and the majority of medically defined hypoglycaemia AEs being mild or moderate in severity that resulted in 2 patient withdrawals.

3.5. Conclusion on safety

Data from the clinical trials are in line with the safety profile of AVANDAMET and continue to show few serious adverse events (SAEs). Patients receiving AVANDAMET in triple oral therapy with a sulphonylurea may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulphonylurea may be necessary.

4. SPC and PL changes: Indication and Posology

In this type II variation the MAH applied to include a triple oral combination indication for AVANDAMET with a sulphonylurea.

The following indication was proposed by the Marketing Authorisation Holder for section 4.1 of the SPC:

"AVANDAMET is indicated in the treatment of type 2 diabetes mellitus:
- *in patients (particularly overweight patients), who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone.*
- *in triple oral therapy in combination with sulphonylurea in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy (see section 4.4.)."*

The CHMP considered the MAH proposed indication to be too widely scoped. The MAH proposal may imply an indication setting of RSG with sulphonylurea in patients that was not supported by clinical trial data by the MAH. In particular, the CHMP noted that no studies were submitted which show the efficacy of the addition of a sulphonylurea to the combination of metformin and rosiglitazone. Therefore, the triple therapy indication of AVANDAMET should be restricted to the addition of rosiglitazone to the combination of metformin and SU.

The CHMP therefore recommend a more concise formulation of the indication in section 4.1 of the SPC. The following wording was proposed by the CHMP for section 4.1 of the SPC:

"AVANDAMET is indicated in the treatment of type 2 diabetes mellitus, particularly overweight patients:
- *who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of metformin*
- *in combination with sulphonylurea in patients (particularly overweight patients) who are unable to achieve sufficient glycaemic control despite receiving metformin and sulphonylurea (triple oral therapy). (See section 4.4.)"*

In addition, the MAH requested a wide scope for section 4.2 of the SPC, which the CHMP also considers to be in need of a smaller scoped definition for the aforementioned reasons.

The following wording for the posology for triple oral therapy was initially proposed by the MAH (section 4.2 of the SPC):

"Triple Oral Therapy (rosiglitazone, metformin and sulphonylurea)

- *Patients on AVANDAMET: the addition of a sulphonylurea at it's recommended starting dose may be considered.*
- *Patients on metformin and sulphonylurea: when appropriate AVANDAMET may be initiated at 4 mg/day rosiglitazone with the dose of metformin substituting that already being taken.*
- *Patients established on triple oral therapy: when appropriate, AVANDAMET may substitute rosiglitazone and metformin doses already being taken.*

Where appropriate, AVANDAMET may be used to substitute concomitant rosiglitazone and metformin in existing dual or triple oral therapy to simplify treatment."

The CHMP recommend a more concise formulation in line with the recommended indication and proposed the following:

"Triple Oral Therapy (rosiglitazone, metformin and sulphonylurea)

- ~~*Patients on AVANDAMET: the addition of a sulphonylurea at it's recommended starting dose may be considered.*~~
- *Patients on metformin and sulphonylurea: when appropriate AVANDAMET may be initiated at 4 mg/day rosiglitazone with the dose of metformin substituting that already being taken.*
- *Patients established on triple oral therapy: when appropriate, AVANDAMET may substitute rosiglitazone and metformin doses already being taken.*

Where appropriate, AVANDAMET may be used to substitute concomitant rosiglitazone and metformin in existing dual or triple oral therapy to simplify treatment."

The restricted wording for the indication and posology sections was addressed in the Request for supplementary information adopted at the July 2005 CHMP. For further discussion on the indication and posology see "request for supplementary information".

4.1. Request for supplementary information

In the request for supplementary information (RSI) adopted at the July CHMP, the MAH was requested to address CHMP concern:

"The presented data do not support the use of the proposed general triple therapy rosiglitazone formulation, but rather support the use of rosiglitazone as an add-on to existing therapy of metformin and/or sulphonylurea derivates. Data presented in earlier applications and to date do not support the triple therapy indication that consists of adding sulphonylurea to existing dual therapy of metformin and rosiglitazone."

In addition the MAH was requested in the RSI to address CHMP's comment with regard to the MAH's proposed wording for the product information including the points discussed in "Indication and Posology".

The MAH provided the following response to the RSI:

Although the MAH have only prospectively studied triple combination therapy with RSG as the third agent initiated, they have some data in a limited number of patients from the RECORD interim study who were failing on dual combination therapy with MET+RSG and who had SU initiated as a third antidiabetic agent. There were 27 patients on MET+RSG who progressed to triple therapy. Data for HbA1c that corresponded with the longest exposure to triple therapy in the largest number of patients was observed between 10 and 18 weeks after initiating triple therapy in 20 patients. In these 20 patients who originally received MET+RSG, the mean HbA1c (± SD) immediately prior to the initiation of SU as part of a triple combination was 8.60 ± 0.8 %. Following 10 to 18 weeks of treatment with triple combination the mean HbA1c reduced by -0.58 %, demonstrating the potential for additional efficacy with triple therapy where a SU is added to existing MET+RGS treatment. Consequently, although limited, there is some useful and reassuring efficacy data relevant to the use of AVANDAMET in a triple therapy setting where a sulphonylurea is added third.

Further reassurance regarding the relevance of order of dosing to efficacy is provided by the scientific literature, which shows that the efficacy outcomes of dual therapy are independent of the order of dosing of the individual components (Charpentier 2002, Setter 2003). In a crossover study (Tosi 2003), patients were initiated on either MET or SU monotherapy and after 6 months had the second antidiabetic agent added to make the dual combination of MET and SU. The achieved improvement in glycaemic control at 12 months was identical irrespective of the order of dosing of the individual components.
Reassurance regarding safety is provided by the order of dosing in the triple therapy studies, which represented a " worse case" scenario with respect to the incidence of AE's since patients were receiving a maximal or near maximal dose of SU prior to the initiation of RSG. Clear advice, particularly within section 4.4 has been proposed within the AVANDAMET SPC to ensure the appropriate and safe management of the patient when introducing a SU in triple therapy. In addition, the MAH proposes the inclusion of a further cross reference to section 4.4, placed after the first triple therapy dosing advice statement in the AVANDAMET SPC.

The MAH acknowledge that the only order of dosing of triple therapy that has been presented in the file is the addition of RSG to a patient failing on dual combination of MET + SU. However the MAH would like to highlight that their position is in line with an observation made for Avandia in the context of the triple oral combination indication that another use of RSG within triple therapy would be in overweight patients failing on MET+RSG who then had a low dose of insulin secretagogue added. Theoretically, this is an appropriate order of dosing as it allows the prescriber to manage patients closely and so minimise the risk of hypoglycaemia.

In conclusion, the MAH maintained that the proposal to add SU at a low dose to patients failing to maintain glycaemic control on AVANDAMET alone is supportable with respect to both efficacy and safety. Furthermore the MAH note that the current approved product information advice for the use of Avandia in triple therapy would permit the addition of a SU to concomitantly administered rosiglitazone and metformin (a dosing scenario directly relevant to the addition of an SU to AVANDAMET). The possibility of dosing in this way with Avandia might logically be expected to translate onto the AVANDAMET SPC. Excluding an indication to add an SU to AVANDAMET might cause confusion to the prescriber in their assessment of the appropriate use of Avandia and AVANDAMET.

CHMP comments and position:

The CHMP commented on the MAH's interpretation of the currently approved Avandia triple therapy indication which reads: "*As triple oral therapy in combination with metformin and a sulphonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy (see section 4.4).*"

One could argue that this indication could be explained in different ways. One may read it as "RSG can be added if glycaemic control with metformin and an SU is insufficient", or one can read it as "triple therapy can be initiated if dual therapy fails, whatever the order of dosing of the individual components". However it should be noted that all studies were performed with RSG as third component added to MET and SU and efficacy was sufficiently demonstrated.

Most type 2 diabetic patients, certainly the diabetics with more or less overweight are nowadays started on metformin treatment. This approach is principally based on the UKPDS study where outcome of patients treated with metformin was better than other treatment modalities but also on the fact that in most type 2 patients an insulin resistance is the prominent pathology. If a patient after this first approach is insufficiently controlled the doctor has a choice between SU and a glitazone. If the patient is obese with an expected concomitant insulin resistance, SU is not the first option and his choice will be giving the patient a glitazone. After this treatment has been successful for a short or long treatment period there will be a time that diabetic control will become insufficient. This will be the case in these patients when pancreatic insulin reserve or production is exhausted. One can expect that the efficacy of SU is relatively less pronounced in these obese patients with higher C-peptide

levels and it is better to treat these obese patients with insulin. So what is required is evidence that SU addition will be successful and certainly as good as insulin treatment. This has not been demonstrated. Limited data were presented from 27 patients who originally received MET+RSG and who had an SU added (RECORD interim study). A decrease in HbA1c was measured in 20 evaluable patients, but data on C-peptide or weight were not mentioned. These data are too limited to draw a conclusion. Solid data on the efficacy of adding a SU to MET+RSG are lacking.

Therefore the CHMP concluded only to approve the indication triple therapy for the use of RSG as an add-on to existing dual therapy of maximally tolerated dose of MET and a SU. The following wording was agreed by CHMP and MAH to be included in section 4.1 of the SPC:

"AVANDAMET is indicated 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.
- in triple oral therapy with sulphonylurea in patients with insufficient glycaemic control despite dual oral therapy with their maximally tolerated dose of metformin and a sulphonylurea (see section 4.4)"

In accordance with the CHMP proposed indication, section 4.2 of the SPC was amended, giving the following posology options for the triple therapy indication:

"Triple Oral Therapy (rosiglitazone, metformin and sulphonylurea) (See section 4.4)
- ~~*Patients on AVANDAMET: the addition of a sulphonylurea at it's recommended starting dose may be considered.*~~
- *Patients on metformin and sulphonylurea: when appropriate AVANDAMET may be initiated at 4 mg/day rosiglitazone with the dose of metformin substituting that already being taken.*
- *Patients established on triple oral therapy: when appropriate, AVANDAMET may substitute rosiglitazone and metformin doses already being taken.*

Where appropriate, AVANDAMET may be used to substitute concomitant rosiglitazone and metformin in existing dual or triple oral therapy to simplify treatment."

The MAH accepted to implement CHMP proposed wording for section 4.2 of the SPC.

4.2. Other SPC and PL changes

As a result of the new triple combination therapy indication for AVANDAMET the MAH proposed to update several sections of the Summary of Product Characteristics to reflect the new safety information. In addition to the updates of sections 4.1 and 4.2 of the SPC, the MAH proposed amendments for sections 4.4, 4.8 of the SPC. These updates as proposed by the MAH have been considered acceptable by the CHMP. The PL has been updated accordingly.

The MAH also applied to update section 5.1 of the SPC to reflect 18-month interim data from a long term ongoing trial for RSG to evaluate the long-term effects of RSG on cardiovascular endpoints and glycaemia. The CHMP was in agreement to include the statement proposed by the MAH in section 5.1 of the SPC.

In addition the MAH applied to include some minor linguistic changes in section 5.2 of the SPC.

4.3. User consultation of the Package Leaflet

Consideration was given for the need of a user consultation test for the Package Leaflet. The MAH provided a justification for not performing such test. The justification of the MAH was considered acceptable for the CHMP.

5. Overall conclusions on benefit - risk

Based on the review of the data on clinical safety and efficacy, the overall benefit/risk is considered positive by the CHMP. The CHMP considers that the variation application for AVANDAMET, to extend the indication to triple therapy with a SU is approvable. However the triple therapy indication is restricted for use of RSG as an add-on to existing dual therapy of maximally tolerated dose of MET and a SU.
The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. CONCLUSION

On 13 October 2005 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.