HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

3 November 2010

AVANDIA 2 mg, film-coated tablets
B/56 (CIP code: 355 353-8)
B/56 (CIP code: 355 355-0)
B/168 (CIP code: 371 696-3)
B/180 (CIP code: 371 698-6)

AVANDIA 4 mg, film-coated tablets
B/28 (CIP code: 355 357-3)
B/56 (CIP code: 355 361-0)
B/84 (CIP code: 371 699-2)
B/90 (CIP code: 371 700-0)

AVANDIA 8 mg, film-coated tablets
B/28 (CIP: 355 363-3)
B/84 (CIP: 371 701-7)
B/90 (CIP: 371 702-3)

rosiglitazone
ATC Code: A10BG02

List I
Date of Marketing Authorisation (centralised procedure): 11 July 2000, renewed 26 May 2010

AVANDAMET 1 mg/500 mg, film-coated tablets
B/112 (CIP code: 363 498-1)
B/336 (CIP code: 371 704-6)
B/360 (CIP code: 371 705-2)

AVANDAMET 2 mg/500 mg, film-coated tablets
B/112 (CIP code: 363 499-8)
B/336 (CIP code: 371 706-9)
B/360 (CIP code: 371 707-5)

AVANDAMET 2 mg/1000 mg, film-coated tablets
B/56 (CIP code: 365 144-2)
B/168 (CIP code: 371 708-1)
B/180 (CIP code: 371 709-8)

AVANDAMET 4 mg/1000 mg, film-coated tablets
B/56 (CIP code: 365 145-9)
B/168 (CIP code: 371 710-6)
B/180 (CIP code: 371 711-2)

rosiglitazone / metformin
ATC Code: A10BD03

List I
Date of Marketing Authorisation (centralised procedure): 20 October 2003

Health Insurance (35%) and hospital use

Applicant: GSK (GlaxoSmithKline)

Reason for request: Re-assessment of Actual Benefit in compliance with article R. 163-21 of the French Social Security Code.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredients

rosiglitazone in AVANDIA products
rosiglitazone / metformin in AVANDAMET products

1.2. Indications

AVANDIA products:
“Rosiglitazone is indicated in the treatment of type 2 diabetes mellitus:

as monotherapy:
- in adults (particularly overweight adults) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance

as dual oral therapy in combination with:
- metformin, in adults (particularly overweight adults) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin
- a sulphonylurea, only in adults who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite monotherapy with a sulfonylurea

as triple oral therapy in combination with:
- metformin and a sulfonylurea, in adults (particularly overweight adults) with insufficient glycaemic control despite dual oral therapy.

For AVANDAMET products (fixed-dose combination of rosiglitazone and metformin):
"treatment of type 2 diabetes mellitus patients, particularly overweight patients:
- who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of 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."

1.3. Dosage (see SPC)

AVANDIA products:
"Rosiglitazone therapy is usually initiated at 4 mg/day. This dose can be increased to 8 mg/day after eight weeks if greater glycaemic control is required. An increase in rosiglitazone to 8 mg/day should be undertaken cautiously following appropriate clinical evaluation to assess the patient's risk of developing adverse reactions relating to fluid retention.
Rosiglitazone may be given once or twice a day (either as one daily dose, or two divided doses).

Special populations
Elderly (≥ 65 years old) (see section 4.4 of the SPC, Fluid retention and cardiac failure)
No dose adjustment is required in the elderly.
Renal impairment (see section 4.4 of the SPC, Fluid retention and cardiac failure)
No dose adjustment is required in patients with mild to moderate renal insufficiency. Limited data are available in patients with severe renal insufficiency (creatinine clearance < 30 ml/min). Rosiglitazone should therefore be used with caution in these patients.
Hepatic impairment
Rosiglitazone must not be used in patients with hepatic impairment.

Paediatric population
There are no data available on the use of rosiglitazone in children under 10 years of age. For children aged 10 to 17 years, there are limited data on rosiglitazone as monotherapy. The available data do not support efficacy in the paediatric population and therefore such use is not recommended."

AVANDAMET products:
"The usual starting dose of AVANDAMET is 4 mg/day rosiglitazone plus 2000 mg/day metformin hydrochloride.
Rosiglitazone can be increased to 8 mg/day after 8 weeks if greater glycaemic control is required. The maximum recommended daily dose of AVANDAMET is 8 mg rosiglitazone plus 2000 mg metformin hydrochloride.
The total daily dose of AVANDAMET should be given in two divided doses.
Dose titration with rosiglitazone (added to the optimal dose of metformin) may be considered before the patient is switched to AVANDAMET.
When clinically appropriate, direct change from metformin monotherapy to AVANDAMET may be considered.
Taking AVANDAMET with or just after food may reduce gastrointestinal symptoms associated with metformin.

Triple oral therapy (rosiglitazone, metformin and a sulphonylurea)
- 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. An increase in rosiglitazone to 8 mg/day should be undertaken cautiously following appropriate clinical evaluation to assess the patient's risk of developing adverse reactions relating to fluid retention.
- 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.
Elderly patients
As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking AVANDAMET should have their renal function monitored regularly.
Patients with renal impairment
AVANDAMET should not be used in patients with renal failure or renal dysfunction e.g. serum creatinine levels > 135 µmol/l in males and > 110 µmol/l in females and/or creatinine clearance < 70 ml/min.
Children and adolescents
AVANDAMET is not recommended for use in children and adolescents below 18 years of age as there are no data available on its tolerance and efficacy in this age group."

1.4. Contraindications:
"Use of rosiglitazone is contraindicated in patients with:
- known hypersensitivity to rosiglitazone or to any of the excipients
- cardiac failure or history of cardiac failure (NYHA class I to IV)
- **an Acute Coronary Syndrome (unstable angina, NSTEMI and STEMI)**
- hepatic impairment.
- diabetic ketoacidosis or diabetic pre-coma."[1]

[1] pioglitazone (ACTOS) is contraindicated in patients with: hypersensitivity to the active substance or any of the excipients; heart failure or history of heart failure (NYHA), hepatic impairment or diabetic ketoacidosis.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

A : Alimentary tract and metabolism
A10 : Drugs used in diabetes
A10B : Blood glucose lowering drugs, excluding insulins
A10BG : Thiazolidinediones
A10BG02 : Rosiglitazone

A : Alimentary tract and metabolism
A10 : Drugs used in diabetes
A10B : Blood glucose lowering drugs, excluding insulins
A10BD : Combinations of oral blood glucose lowering drugs
A10BD03 : Rosiglitazone / metformin

2.2. Medicines in the same therapeutic category

Other proprietary glitazones on the list of reimbursable products:

- as monotherapy, in type 2 diabetic patients who show intolerance to metformin or for whom metformin is contraindicated and who are inadequately controlled by diet and lifestyle measures: ACTOS (pioglitazone)

- as dual oral therapy:
  - in combination with metformin, in type 2 diabetic patients (particularly overweight patients), inadequately controlled despite maximum tolerated dose of metformin: ACTOS (pioglitazone), COMPETACT (fixed-dose pioglitazone / metformin combination)

  - in combination with a sulfonylurea only in the case of contraindication or intolerance to metformin in patients inadequately controlled despite maximum tolerated dose of a sulfonylurea: ACTOS (pioglitazone)

  - as triple oral therapy: ACTOS (pioglitazone)

2.3. Medicines with a similar therapeutic aim

- as oral monotherapy, in the case of contraindication or intolerance to metformin in patients with type 2 diabetes whose disease is inadequately controlled by diet and lifestyle measures:
    - intestinal alpha-glucosidase inhibitors
    - sulfonylureas
    - glinides
    - dipeptidyl peptidase-4 (DPP4) inhibitors; *sitagliptin-based products have been granted an indication as monotherapy but have not yet been evaluated by the Committee*

- as dual therapy:

- in patients with type 2 diabetes who are not achieving adequate glycaemic control despite maximal tolerated doses of oral monotherapy with metformin:
    - sulfonylureas
    - intestinal alpha-glucosidase inhibitors
    - glinides
    - dipeptidyl peptidase-4 (DPP4) inhibitors
    - parenteral incretin mimetics

- in type 2 diabetic patients with inadequate glycaemic control despite maximal tolerated doses of oral sulfonylurea monotherapy *who show intolerance to metformin or for whom metformin is contraindicated:*
    - intestinal alpha-glucosidase inhibitors
    - dipeptidyl peptidase-4 (DPP4) inhibitors
    - parenteral incretin mimetics (in combination with a sulfonylurea)

- as triple oral therapy: in type 2 diabetic patients with inadequate glycaemic control despite metformin and a sulfonylurea at maximum tolerated doses:
    - insulin
    - parenteral incretin mimetics
    - dipeptidyl peptidase-4 (DPP4) inhibitors; *only sitagliptin is indicated as part of a triple therapy*

3. SUMMARY OF PREVIOUS TRANSPARENCY COMMITTEE OPINIONS

AVANDIA 2 mg, 4 mg, 8 mg, film-coated tablets (rosiglitazone)

Committee Opinion dated 22 November 2000

For the indication: As **dual oral therapy**, in combination with metformin or a sulfonylurea

Actual clinical benefit: Given the indications granted to rosiglitazone, a comparison with the combination of metformin + a sulfonylurea (in patients for whom metformin is not contraindicated) would be useful in order to assess the utility of this new oral diabetes drug.
The actual benefit of AVANDIA is **substantial**.

Improvement in actual clinical benefit: In view of the current data and in particular in the absence of a comparative study with the usual antidiabetic combinations, **the Transparency Committee is unable to set a level of improvement in actual benefit** compared to currently available treatments for the sub-groups of patients with diabetes who are covered by the marketing authorisation.

Committee Opinion dated 24 March 2004

For the indication: **as a monotherapy** for patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance.

Actual benefit: **substantial**
Improvement in actual benefit V in comparison with glibenclamide (on the basis of one randomised comparative double-blind non-inferiority study versus glibenclamide).

Committee Opinion dated 31 May 2006

For the indication: **as triple oral therapy** in combination with metformin and a sulfonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.
Actual benefit: The actual benefit of AVANDIA is **substantial**.

IAB: AVANDIA, as triple oral therapy in combination with metformin and a sulfonylurea, **does not provide an improvement in actual benefit (level V)**, but represents an additional tool in the management of patients with type 2 diabetes with insufficient glycaemic control despite a metformin + sulfonylurea combination. Adding rosiglitazone to dual therapy associating metformin and a sulfonylurea only results in a small reduction in HbA1c.

Committee Opinion dated 15 October 2008
(re-assessment of AB and IAB, renewal of registration of AVANDIA products)

AB in all indications: Given the available data, particularly tolerance data, the actual clinical benefit is **moderate**.
IAB: Given the new efficacy and tolerance data, AVANDIA products do not provide an improvement in actual benefit (**IAB V**) in the management of patients with type 2 diabetes treated by monotherapy or dual or triple oral therapy, in comparison with the currently available oral antidiabetics.

AVANDAMET 1 mg / 500 mg, 2 mg / 500 mg, 2 mg / 1000 mg, 4 mg / 1000 mg, film-coated tablets (rosiglitazone maleate / metformin hydrochloride)

Committee Opinion dated 7 April 2004

- AVANDAMET is indicated in the treatment of patients with type 2 diabetes, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone.

Actual benefit: substantial
IAB V in comparison with non-fixed-dose combination of the same 2 active substances.

Committee Opinion dated 31 May 2006

- AVANDAMET is indicated in the treatment of patients with type 2 diabetes mellitus, particularly overweight patients, in triple oral therapy with a sulphonylurea in patients with insufficient glycaemic control despite dual oral therapy with their maximally tolerated dose of metformin and a sulphonylurea.

Actual benefit: substantial
IAB: AVANDAMET, a fixed-dose combination of rosiglitazone and metformin, does not provide an improvement in actual benefit (IAB V) in comparison with a non-fixed-dose combination of the two active substances.

Committee Opinion dated 15 October 2008 (re-assessment of AB and IAB)

AB in all its indications: Given the available data, particularly tolerance data, the actual benefit is **moderate**.
IAB: A review of this new efficacy and tolerance data shows that AVANDAMET products do not provide an improvement in actual benefit (**IAB V**) in the management of patients with type 2 diabetes treated with dual or triple oral therapy, in comparison with the currently available oral antidiabetics.

4. ANALYSIS OF DATA MADE AVAILABLE SINCE PREVIOUS OPINION

Following the publication of tolerance data for rosiglitazone products, particularly concerning cardiovascular tolerance, the Transparency Committee wished to re-evaluate these products. The firm was informed in a letter dated 15 July 2010 that it should provide all data that would enable a re-assessment of the actual benefit of these products.

The Transparency Committee, in line with article R.163-21 of the Social Security Code, has taken responsibility for re-assessment of AVANDIA and AVANDAMET products, independently of the outcome of the possible suspension of marketing authorisation for these products by the European and French authorities, and regardless of whether or not such a suspension may be lifted in the future.

The firm duly provided 2 efficacy studies in the dossier it submitted on 9 September 2010:
- the ADOPT study, which had previously been examined by the Committee and the conclusions of which will be summarised in this document (see opinion dated 15 October 2008 for detailed results);
- the RECORD study, with results at 5.5 years. In 2008, the Committee analysed the results of the interim analysis at 18 months.

The tolerance data provided were:
- results of the RECORD study at 5.5 years;
- summary of the results of meta-analyses that were analysed in 2008, and updates to these (meta-analyses by Nissen, the FDA and GSK).
- results of retrospective observational studies[2, 3, 4, 5, 6, 7] which will not be described in this document, as the data are not transferable (patient characteristics are different to those followed up in France, and different therapeutic management procedures were used).

[2] Graham DJ, Ouellet-Hellstrom R, MaCurdy TE et al. Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone JAMA. published online Jun 28, 2010; (doi:10.1001/jama.2010.920).
[3] Loebstein R et al. Database Evaluation of the Effects of Long-Term Rosiglitazone Treatment on Cardiovascular Outcomes in Patients With Type 2 Diabetes J Clin Pharm OnlineFirst, published on May 19, 2010 as doi:10.1177/0091270010368281.
[4] Juurlink DN et al. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study BMJ 2009;339:b2942.

Results of the AVANCE observational study, which was carried out in France, requested by the Committee in its opinion dated 24 March 2004.

9 studies, including:

- the BARI 2D study[8] (Bypass Angioplasty Revascularization Investigation 2 Diabetes), the aim of which was to evaluate the cardiovascular benefit of two different treatment strategies in patients with both diabetes and heart disease, initially comparing a surgical procedure (prompt revascularisation with PCI or coronary artery bypass) with intensive medical treatment for heart disease in terms of reduction in mortality, and subsequently comparing insulin sensitisation treatment (metformin and/or glitazone) with insulin provision (insulin or sulfonylureas).

- the REFLECT-2 and REFLECT-5 studies[9], the aim of which was to evaluate the effects of prolonged-release rosiglitazone (a formulation that is not available in France), as an adjuvant treatment to donepezil, on cognitive capacity and overall clinical response in patients with mild-to-moderate Alzheimer's disease.

- the DREAM study[10] (Diabetes REduction Assessment with ramipril and rosiglitazone Medication), which had previously been submitted in 2008, which evaluated the effect of rosiglitazone or ramipril versus placebo on the progression of type 2 diabetes in patients with impaired glucose tolerance;

- the STARR study[11] (STudy of Atherosclerosis with Ramipril and Rosiglitazone), the aim of which was to evaluate the effects of rosiglitazone versus ramipril on internal carotid artery intima media thickness in patients with impaired glucose tolerance;

- the APPROACH study[12] (Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in patients with type 2 diabetes mellitus with Cardiovascular History), the aim of which was to compare the effects of rosiglitazone versus a sulfonylurea (glipizide) on the progression of coronary atherosclerosis in patients with type 2 diabetes;

- the VICTORY study[13] (VeIn Coronary aTherOsclerosis and Rosiglitazone after bypass surgerY), the aim of which was to evaluate the effect of rosiglitazone on prevention of progression of atherosclerosis in saphenous vein bypass grafts in patients with diabetes who had undergone coronary bypass.

These studies will not be described, as they did not specifically evaluate rosiglitazone in the indications given in the MA, and (in the case of the APPROACH and VICTORY studies) they involved intermediate endpoints.

- the ACCORD study[14] (Action to Control CardiOvascular Risk in Diabetes), the aim of which was to evaluate the effects of 2 management strategies for patients with type 2 diabetes (so-called "intensive" strategy versus the standard strategy) on the rate of major cardiovascular adverse events in patients with cardiovascular risk factors. This study will not be described here, as the results specific to patients treated with rosiglitazone are not

[5] Stockl KM et al. Risk of acute myocardial infarction in patients treated with thiazolidinediones or other antidiabetic medications. Pharmacoepidemiology and drug safety 2009; 18: 166-174

[6] Wertz DA et al. Risk of Cardiovascular Events and All-Cause Mortality in Patients Treated With Thiazolidinediones in a Managed Care Population. Circ Outcomes. 2010;3.

[7] Bilik D et al. Thiazolidinediones, cardiovascular disease and cardiovascular mortality: translating research into action for diabetes (TRIAD). Pharmacoepidemiology and drug safety 2010; 19: 715-721

[8] The BARI 2D Study Group. A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease. NEJM 2009;360(24):2503-15.

[9] Gold M, Alderton C et al. Rosiglitazone Monotherapy in Mild-to-Moderate Alzheimer's Disease: Results from a Randomized, Double-Blind, Placebo-Controlled Phase III Study Dement Geriatr Cogn Disord 2010;30:131–146

[10] DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effects of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose : a randomised controlled trial. The Lancet. 2006; 368 (9541): 1096-105.

[11] Lonn EM et al. Effect of Ramipril and of Rosiglitazone on Carotid Intima-Media Thickness in People With Impaired Glucose Tolerance or Impaired Fasting Glucose STARR (STudy of Atherosclerosis with Ramipril and Rosiglitazone). J Am Coll Cardiol 2009;53:2028–35

[12] Gerstein HC, Ratner RE, Cannon CP et al. Effect of Rosiglitazone on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease. Circulation 2010;121:1176-1187

[13] Bertrand OF, Poirier P, Rodés-Cabau J et al. Cardiometabolic effects of rosiglitazone in patients with type 2 diabetes and coronary artery by passgrafts: A randomized placebo-controlled clinical trial. Atherosclerosis 2010 DOI:10.1016/j.atherosclerosis.2010.06.005.

[14] The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of Intensive Glucose Lowering in Type 2 Diabetes. NEJM 2008;358:2545-59.

available, and the target glucose levels[15] for both strategies do not correspond to the recommended targets for France. In addition, this study was stopped after 3.5 years following an increase in mortality in the intensive treatment arm.

- the VADT study[16] (Veterans Affairs Diabetes Trial), the aim of which was to evaluate the effect of 2 management strategies for type 2 diabetes (a so-called "intensive" strategy versus a standard strategy) on cardiovascular events in patients with type 2 diabetes with high levels of cardiovascular risk. This study will not be described here, as the results specific to patients treated with rosiglitazone are not available, and the target glucose levels[17] for both strategies do not correspond to the recommended targets for France.

Only comparative studies carried out using the indications given in the MA and which enable assessment of the benefits and tolerance profile of AVANDIA and AVANDAMET products using clinical criteria will be described in the present document: these are the ADOPT and RECORD studies, the 3 meta-analyses mentioned above and the AVANCE post-marketing study.

4.1. Efficacy

4.1.1. ADOPT study[18]

The objective of this randomised double-blind study, which has previously been evaluated by the Committee, was to evaluate efficacy and long-term tolerance (4-6 years) of rosiglitazone as a monotherapy in comparison with metformin or a sulfonylurea (glibenclamide) in 4351 patients with type 2 diabetes who had been diagnosed during the previous 3 years, not previously treated, with fasting blood glucose of between 1.26 and 2.40 g/L.

NB: the conclusions of the Committee in its opinion dated 15 October 2008 were as follows: *"a statistically significant difference, with rosiglitazone being superior to the two other treatment arms, was observed for the primary endpoint (failure of monotherapy at 5 years)[19]. However, the usefulness of this way of measuring this endpoint is arguable. Monotherapy failure is measured using glycaemia values and not using glycosylated haemoglobin, which is the value that is best correlated with the risk of complications. "*

4.1.2. RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes)[20, 21]

This phase IV study, lasting 6 years, was requested by the EMA as a way of evaluating the impact of AVANDIA in combination with metformin or a sulfonylurea (glibenclamide, gliclazide or glimepiride) on cardiovascular events and blood glucose levels in comparison with the current standard dual therapy (metformin and a sulfonylurea) using non-inferiority hypotheses.

[15] In the so-called "intensive" strategy, the target is HbA1c of <6%. In the standard strategy, the HbA1c level should be between 7 and 7.9%.

[16] Duckworth W, Abraira C, Moritz T et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. NEJM 2009;360:129-39.

[17] In the so-called "intensive" strategy, the target is HbA1c of <6%. In the standard strategy, the HbA1c level should be between 8 and 9%.

[18] Most recent publication: Kahn S E. et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006; 355 : 2427-43

[19] characterised by fasting glycaemia > 1.80 g/l (10 mmol/l) confirmed on consecutive measurements, after at least 6 weeks of treatment with the maximum tolerated dose of the product.

[20] P.D. Home et al. Rosiglitazone RECORD study: glucose control outcomes at 18 months. 2007 Diabetes UK. Diabetic medicine, 24, 626 - 634

[21] Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJV, for the RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009 DOI:10.1016/S0140-6736(09)60953-3.

In 2008, the Committee received the results of an interim analysis at 18 months, which was planned for in the protocol, concerning efficacy in terms of blood glucose control (secondary endpoint, n=1122 patients). At 18 months it was shown that rosiglitazone in combination with metformin or a sulfonylurea was non-inferior to dual oral therapy with metformin + sulfonylurea in terms of reduction in HbA1c. However, the differences observed in comparison with the combination metformin + a sulfonylurea in terms of reduction in HbA1c were modest.
At 5.5 years, the differences observed in terms of reduction in HbA1c level were small:
- 0.26% between the rosiglitazone + sulfonylurea combination and the metformin + sulfonylurea combination, p<0.0001;
- 0.29% between the rosiglitazone + metformin combination and the metformin + sulfonylurea combination, p<0.0001;

4.2. Adverse effects

4.2.1. RECORD study [22]:

Conclusions of the 2008 re-assessment
In June 2007, after the publication of Nissen's meta-analysis which showed that there was an increased risk of myocardial infarction and cardiovascular death due to rosiglitazone, the working group for the RECORD study published the results of an interim analysis (not initially planned for in the protocol) of cardiovascular events and deaths in patients on rosiglitazone.

The RECORD study is a randomised open-label trial to assess the efficacy of rosiglitazone in the primary prevention of cardiovascular events in 4,447 patients with type 2 diabetes (2,220 on metformin + rosiglitazone, 2,227 on metformin + sulfonylurea). Interim analysis was carried out after a mean follow-up of 3.75 years. The primary endpoint was time to occurrence of the first cardiovascular event, defined as either hospital admission due to a cardiovascular cause (including myocardial infarction, cardiac failure, CVA, unstable angina, transient ischaemic attack, unplanned revascularisation) or death from a cardiovascular cause (including myocardial infarction, cardiac failure, CVA, sudden death syndrome, other acute cardiovascular events, other causes of cardiovascular mortality, unknown cause of death).

No statistically significant difference was demonstrated between the rosiglitazone group and the control group in terms of the composite endpoint.
Patients in the rosiglitazone group have a statistically higher risk of congestive heart failure than patients in the control metformin + sulfonylurea group (HR=2.24, 95% CI [1.27, -3.97], p=0.006).

Updated data
Rosiglitazone was to be considered as non-inferior to the control substance if the upper limit of the 95% confidence interval of the relative risk of occurrence of an initial cardiovascular event (primary endpoint) was <1.20.
At 5.5 years, the relative risk of occurrence of an initial cardiovascular event was 1.03, 95% CI [0.86; 1.23] in the per-protocol population. Non-inferiority was therefore not demonstrated.
No difference was observed between the treatment arms in terms of occurrence of myocardial infarction, CVA or cardiovascular mortality, but the relative risk of congestive heart failure was greater in those on rosiglitazone (HR=2.10, 95% CI [1.35;3.27], p=0.001).
In this study, which established the fracture risk in 2007, long-term analysis confirmed that there was a higher incidence of fractures: RR=1.57, 95% CI [1.26;1.97], p<0.001.

[22] P.D. Home *et al*. Rosiglitazone evaluated for cardiovascular outcomes – an interim analysis. N Engl J Med 2007; 357 : 1-11

4.2.2. Other data specific to cardiovascular tolerance:

Several meta-analyses of randomised trials have examined the effect of glitazone treatment on cardiovascular mortality and the incidence of events linked to myocardial ischaemia.

GSK meta-analysis:

Summary of conclusions of 2008 Transparency Committee re-assessment

In August 2005, GSK carried out, using its clinical trials registry, a meta-analysis of 42 randomised trials (14,237 patients) comparing rosiglitazone with placebo or another oral antidiabetic agent (metformin or a sulfonylurea). The aim was to assess the risk of patients developing or experiencing worsening of cardiac ischaemia on rosiglitazone. More than 70% of patients included in these trials had no known cardiovascular disease. The overall incidence of specific events associated with myocardial ischaemia was higher for treatment strategies including rosiglitazone than for comparator treatments (placebo, metformin, sulfonylureas), at 1.99% compared with 1.51% (HR=1.31, 95% CI [1.01; 1.70]).
After the publication in 2006 of the ADOPT trial, a long-term trial involving 4,360 patients, the results of this trial were combined with those in the previous meta-analysis. After incorporation of these results, the risk of myocardial infarction remained significantly increased for rosiglitazone (RR: 1.46; 95% CI [1.01;2.1]), with no statistically significant change in cardiovascular mortality.

Updated data

Ten additional trials were included in the updated meta-analysis (giving a total of 16,995 patients).
The primary endpoints remained: assessment of the risk of myocardial ischaemic events and risk of occurrence of major cardiovascular adverse events (a composite endpoint that included cardiovascular death, myocardial infarction and non-fatal CVAs).
In the rosiglitazone arm, in comparison with comparator treatments, the relative risk of occurrence of myocardial ischaemic events was 1.09, 95% CI [0.89;1.35], and that of major cardiovascular adverse events was 1.12, 95% CI [0.79;1.59].

Meta-analysis by Nissen[23]:

Summary of conclusions of 2008 Transparency Committee re-assessment

This meta-analysis of 42 randomised trials (27,847 patients) comparing rosiglitazone versus placebo or another oral antidiabetic agent showed a significantly increased risk of myocardial infarction for rosiglitazone (HR=1.43; 95% CI [1.03;1.98], p=0.03), with no statistically significant change in cardiovascular mortality.

Updated data

The update to this meta-analysis[24], which was published in 2010, confirms the previously observed results.
This updated meta-analysis included 56 clinical studies (35,531 patients, of whom 19,509 were treated with rosiglitazone, with a mean age of 57.1 years and a mean HbA1c level of 8.2% at the time of inclusion). Analysis of studies in which at least one event was observed showed that there was a statistically significant increase in the risk of myocardial infarction in patients receiving rosiglitazone than in the control arm (OR=1.28, 95% CI [1.02;1.63], p=0.04 if the results of the RECORD study are taken into account, OR=1.39, 95% CI [1.02;1.89], p=0.04 if the results of the RECORD study are not taken into account).
No difference was observed in terms of cardiovascular mortality.

[23] Nissen SE *et al*. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007; 356 : 1-15
[24] Nissen SE, Wolski K. Rosiglitazone Revisited An Updated Meta-analysis of Risk for Myocardial Infarction and Cardiovascular Mortality. Arch Intern Med 2010

FDA meta-analysis:

Summary of conclusions of 2008 Transparency Committee re-assessment
In July 2007, the FDA presented the results of a meta-analysis of 42 double-blind randomised trials (14,237 patients). According to this meta-analysis, the risk of events linked to myocardial ischaemia was significantly higher for rosiglitazone (HR: 1.4; 95% CI [1.1;1.8]) than for comparator treatments, mainly placebo. The odds ratio of occurrence of major cardiovascular adverse events (a composite endpoint including cardiovascular mortality and all-cause mortality, incidence of CVA, myocardial infarction, myocardial ischaemic events and cardiac failure) in patients receiving rosiglitazone in comparison with comparators was 1.2, 95% CI [0.8;1.9].

Updated data
In 2010, the FDA updated its meta-analysis[25] to include the same 10 clinical studies that GSK added to its own meta-analysis (giving a total of 16,995 patients). The comparator was a placebo in 46 of the 52 studies.
The odds ratio for the occurrence of major cardiovascular adverse events in patients receiving rosiglitazone in comparison with the control group was 1.44, 95% CI [0.95; 2.20].
No difference was observed in cardiovascular mortality or CVA frequency.
However, the analysis showed:
- an increase in the risk of myocardial infarction: OR=1.80, 95% CI [1.03; 3.25]
- an increase in events linked to myocardial ischaemia: OR=1.34, 95% CI [1.07; 1.70]
- an increase in the risk of cardiac failure: OR=1.93, 95% CI [1.30; 2.93].

In the United States, the FDA[26] identified 7 case-control studies and 14 cohort studies that showed that rosiglitazone carried a higher cardiovascular risk than pioglitazone. The current situation is that the FDA has revised its information on the use of rosiglitazone to contain a warning.

4.2.3. Changes to the tolerance information in the SPC:

The SPCs for AVANDIA and AVANDAMET products were amended in March 2008, with revisions to the Special Warnings and Precautions for Use chapter of the SPC (with extra warnings about fluid retention & cardiac failure and weight gain).
The main changes concerned the increased incidence of cardiac failure when rosiglitazone is given in combination with insulin, contraindication of rosiglitazone in patients with acute coronary syndrome, the fact that rosiglitazone should be used with care in patients with ischaemic heart disease, and the risk of upper limb and distal lower limb fractures.
Since then, the SPCs have been amended again, particularly section 4.8 "Undesirable effects" and 5.1 "Pharmacodynamic properties", which include data from the ADOPT and RECORD studies, and the results of the meta-analysis carried out by GSK concerning cardiovascular tolerance and fracture risk.

[25] Callaghan F. Rosiglitazone Cardiovascular Safety Meta-Analysis. FDA. Joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. July 13-14, 2010.
[26] Food and Drug Administration. Briefing document: July 13-14, 2010 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. (http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm191113.htm)

4.2.4. Main data from PSUR and national pharmacovigilance systems

Available international pharmacovigilance data from PSURs (Periodic Safety Update Reports) cover the period 26 May 2007 to 25 May 2010 for AVANDIA and 11 October 2007 to 10 October 2009 for AVANDAMET.
The following were observed:
- 1067 cases of ischaemic cardiac events for AVANDIA and 138 for AVANDAMET. The majority of patients (94%) had one or more risk factors for occurrence of an ischaemic cardiac event independently of rosiglitazone treatment (hypertension, hypercholesterolaemia, obesity, coronary artery disease, history of myocardial infarction and/or revascularisation, smoking, family history of premature death caused by myocardial infarction).
- 93 cases of fractures in patients receiving AVANDIA and 19 for those receiving AVANDAMET.

Analysis of spontaneous notifications nationally between 1 July 2007 and 31 July 2010 showed that the most commonly notified effects were oedema (mainly peripheral oedema), weight gain, cardiac failure, shortness of breath, anaemia, macular oedema with associated impaired vision, and gastrointestinal disorders in patients taking AVANDAMET (related to metformin consumption).

4.3. Results of ADVANCE post-marketing study

The AVANCE post-marketing study was requested by the Transparency Committee and CEPS in order to provide a description of actual conditions in which rosiglitazone was used by general practitioners and specialists, and in order to evaluate the efficacy of this treatment, the characteristics of patients treated with it, conformity with the SPC, compliance and tolerance.
During this study, 1097 patients were enrolled by 298 doctors. Enrolled patients had a mean age of 61.1 years, 57% were male, and mean time since diabetes diagnosis was 7.5 years. In addition, 42.6% were obese and 43.8% overweight. Renal failure (creatinine clearance < 60 mL/minute) was observed in 12.4% of patients. Cardiovascular involvement was reported for 26% of patients enrolled (hypertension: 9.8%, coronary artery disease: 7.3%, heart failure: 3.2%, lower limb artery inflammation: 2.6% and carotid artery stenosis: 1.6%).
Mean HbA1c levels at time of inclusion was 8.0% (40% of patients had HbA1c > 8%). 51.9% of patients were receiving dual oral therapy, 29.6% triple therapy, 16.4% monotherapy and 2% quadruple therapy or therapy including insulin.
Overall, the indications given in the SPC were adhered to for 758 of the 1097 patients included (69.1%). Serious misuse (failure to adhere to contraindications such as cardiac failure and liver cytolysis) was identified in 6.7% of patients.
After treatment, the proportion of patients with "HbA1c <8%" and/or "reduction in HbA1c of at least 0.7 points" was between 85% and 90%, depending on the follow-up visit and the specialism of the investigator.
Treatment switch (stopping rosiglitazone and prescription of insulin at the same follow-up appointment) was observed for 6.1% of patients (10.3% of those seen by specialists and 3.4% of those seen by generalists).
A tolerance analysis was done using 2 approaches: the first was limited to analysis of spontaneous notifications of AEs, as initially provided for in the protocol (54 patients affected, i.e. 5.2% of the patients in the tolerance population), and the second was a more active approach to counting AEs, which was adopted because of the lack of spontaneous notification of events that were observed in patient records and that would have been expected with rosiglitazone (148 patients affected, or 14.3%). The frequency of adverse effects that led to change or cessation of treatment was 4.4% using spontaneous notification as the measure, and 11.5% (n=119) using spontaneous and solicited notifications as the measure.

Apart from gastro-intestinal effects (which are linked not to rosiglitazone but to the metformin that is contained in AVANDAMET), the most common effects were the known effects of glitazones: peripheral oedema, weight gain, cardiac failure, dyspnoea associated with weight gain or sign/symptom of cardiac failure, headaches, myalgia, dizziness and anaemia.
Cardiac failure was reported for 26 patients in total, i.e. 2.5% of the cohort. The mean age of these patients was higher than for the cohort as a whole, and these patients had factors that predisposed them to cardiac failure. Of the 26 cases of cardiac failure, 14 (1.3% of the patients in the cohort) had one criterion for severity.

Eight patients (0.8% of the tolerance population) developed non-fatal ischaemic cardiac events during the study. All these patients had at least one cardiovascular risk factor apart from diabetes.
At 24 months, 70.3% (95% CI = [67.3%; 73.3%]) of patients were still being treated with rosiglitazone.
Rosiglitazone compliance was considered to be complete for 85-91% of patients depending on the investigator and 80-89% depending on the patient.

In general, the conditions for use of rosiglitazone were adhered to, and the tolerance profile was in line with that expected for this product.

4.4. Conclusion

- **in terms of efficacy**

Since the most recent opinion issued by the Committee, new data relating to efficacy have been provided. These are the final results of the RECORD study, in which, at 5.5 years, there was a statistically significant but weak result showing that rosiglitazone in combination with metformin or a sulfonylurea provided better results in terms of reduction in HbA1c than the standard metformin + sulfonylurea combination.

- **in terms of tolerance**

- In 2008, the Committee examined four meta-analyses which evaluated the risk of myocardial infarction and myocardial ischaemia in rosiglitazone treatment. These meta-analyses primarily involved the same randomised trials. All four showed that rosiglitazone carried a statistically significant increase in the risk of myocardial infarction or cardiac ischaemia. None of the meta-analyses demonstrated a reduction in cardiovascular mortality for rosiglitazone.
The data indicated that an increased risk of myocardial infarction and cardiac ischaemia associated with rosiglitazone could not be ruled out. A new risk had been identified for patients on rosiglitazone treatment: fractures. This set of information led the Committee to downgrade the Actual Benefit of AVANDIA and AVANDAMET products from substantial to moderate.

- In 2010, an update to the data from the RECORD study confirmed that there was a greater risk of congestive heart failure (HR = 2.10, 95% CI [1.35;3.27]) and a greater incidence of fractures (RR = 1.57, 95% CI [1.26; 1.97]) in those receiving rosiglitazone in relation to comparator products.

Updates to the various meta-analyses confirmed that rosiglitazone carried an increased risk of myocardial infarction (Nissen's meta-analysis) and an increase in the risk of events linked to myocardial ischaemia (FDA meta-analysis). The update to the FDA meta-analysis showed that there was an increase in the risk of myocardial infarction and cardiac failure.
Conversely, the increased risk of myocardial infarction and events associated with cardiac ischaemia that had previously been observed in the GSK meta-analysis was not repeated. However, the upper limits of the 95% confidence intervals mean that an increased cardiovascular risk cannot be ruled out for rosiglitazone. *(see table below)*

Summary table of the relative risks of occurrence of cardiovascular events in the various meta-analyses available in 2010

Cardiovascular risks	Nissen HR (95% CI)	FDA HR (95% CI)	GSK HR (95% CI)
Myocardial infarction	1.28 (1.02; 1.63)	1.80 (1.03; 3.25)	1.41 (0.89; 2.22)
Cardiovascular mortality	1.03 (0.78; 1.36)	1.46 (0.60; 3.77)	1.26 (0.62; 2.57)
Major cardiovascular adverse events	-	1.44 (0.95; 2.20)	1.12 (0.79; 1.59)
CVA	-	0.86 (0.40; 1.83)	0.63 (0.33; 1.19)
Severe and non-severe myocardial ischemia	-	1.34 (1.07; 1.70)	1.09 (0.89; 1.35)

On 23 September 2010, the EMA and AFSSAPS recommended the suspension of marketing authorisation for rosiglitazone-based products, following a re-assessment of these products by the European Committee for Medicinal Products for Human Use (CHMP) which concluded that the risk/benefit ratio was unfavourable: the increase in cardiovascular risk, primarily myocardial infarction and stroke, did not outweigh the expected benefits in terms of reduction in glycaemia.

Just one meta-analysis has been done to assess the effect of pioglitazone (the other available glitazone) on the incidence of myocardial infarction. According to this meta-analysis, it is unlikely that pioglitazone increases the risk of myocardial infarction[27]. According to another more recent meta-analysis, pioglitazone does not appear to be associated with an increase in the risk of occurrence of cardiovascular events[28].

[27] Lincoff M *et al*. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus. A meta-analysis of randomised trials. JAMA 2007;298:1180-8.
[28] Manucci E *et al*. Pioglitazone and cardiovascular risk. A comprehensive meta-analysis of randomized clinical trials. Diabetes, Obesity and Metabolism 2008;10:1221–1238.

5. TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Re-assessment of Actual Benefit provided by AVANDIA and AVANDAMET products in all indications of the marketing authorisation:

- "as oral monotherapy, in patients (particularly overweight patients) for whom metformin is inappropriate because of contraindications or intolerance (only for AVANDIA)
- as dual oral therapy, in combination with metformin, in particular in overweight patients with insufficient glycaemic control despite metformin given as monotherapy, or in combination with a sulfonylurea in patients who show intolerance to metformin or for whom metformin is contraindicated
- as triple oral therapy, in combination with metformin and a sulfonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy."

Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular complications.
AVANDIA and AVANDAMET products are intended to treat hyperglycaemia.

Efficacy/adverse effect ratio:
Rosiglitazone-based products have modest efficacy in terms of glycaemic control.
The adverse effects observed for rosiglitazone are those that are generally observed for glitazones (e.g. oedema, weight gain, fractures) with the exception of the cardiovascular risk (myocardial ischaemia) which is greater for rosiglitazone. Given the data described in section 4.2 "Adverse effects", rosiglitazone is associated with an increase in cardiovascular risk. New tolerance data have confirmed this poor tolerance profile, showing an increase in the risk of myocardial infarction, cardiac failure and an increased risk of events linked to myocardial ischaemia.
There are no solid arguments suggesting a reduction in cardiovascular risk, which is one of the main aims of diabetes treatment.
The efficacy/adverse effect ratio of AVANDIA and AVANDAMET products is therefore negative.

Therapeutic use
The aims of therapeutic management of diabetes are glycaemic control: control of HbA1c and control of associated risk factors.

According to the guideline “Medication for type 2 diabetes” published by AFSSAPS and HAS in November 2006, initial treatment of type 2 diabetes is based on an assessment of and realistic changes to lifestyle (diet and exercise). The adoption of an active lifestyle and nutritional planning are essential interventions at all stages of diabetes management.
Oral blood glucose lowering drugs are prescribed when diet and lifestyle changes (DLC) are no longer sufficient to control blood glucose levels: HbA1c > 6%. There are 4 classes: metformin, intestinal alpha-glucosidase inhibitors (AGI), insulin secretors, glitazones.
These guidelines are currently being updated, and do not include five antidiabetic agents which received MA after 2006: two GLP-1 inhibitors, exenatide (MA November 2006) and liraglutide (MA June 2009), three DPP-4 inhibitors, sitagliptin (MA March 2007), vildagliptin (MA September 2007) and saxagliptin (MA October 2009).

The different stages of treatment are summarised in the table below.

Therapeutic strategy (LTC 8 - Type 2 Diabetes)[29]

HbA1c levels	Treatment	Target HbA1c
HbA1c between 6% and 6.5% despite DLC	Metformin monotherapy (or AGI if metformin is poorly tolerated or contraindicated)	< 6.5%
HbA1c > 6.5 % despite DLC	Metformin monotherapy or insulin secretor or AGI	Maintain HbA1c < 6.5%
HbA1c > 6.5% despite monotherapy and DLC	Dual therapy*	Reduce HbA1c < 6.5%
HbA1c > 7% despite dual oral therapy and DLC	Triple oral therapy: metformin + insulin secretor + glitazone or - insulin + metformin ± other OAD except glitazone	Reduce HbA1c < 7%
HbA1c > 8% despite triple therapy and DLC	Insulin + metformin ± other OAD except glitazone	Reduce HbA1c < 7%

DLC: diet and lifestyle changes; OAD: oral antidiabetics; AGI: intestinal alphaglucosidase inhibitors
* metformin + insulin secretor (sulfonylurea or glinide), metformin + glitazone, metformin + alphaglucosidase inhibitor, insulin secretor + glitazone, or insulin secretor + alphaglucosidase inhibitor.

The two main aims of treatment for type 2 diabetes are to reduce the complications of microangiopathy and macroangiopathy. Rosiglitazone plays no role in the second aim.
There is another drug in the same therapeutic class (pioglitazone), which does not carry the same increased risk of cardiovascular complications that is observed for rosiglitazone. There are therefore few arguments in favour of the use of rosiglitazone in the treatment of type 2 diabetes.

In addition, the most recent guidelines of the EASD (European Association for the Study of Diabetes) and the ADA (American Diabetes Association)[30] excluded rosiglitazone from their treatment algorithms.

For this reason, given the available information and treatment alternatives, AVANDIA and AVANDAMET products no longer have a role in therapeutic strategies for the treatment of diabetes.

Public Health Benefit:
The available data confirm that no public health benefit was attributed to AVANDIA and AVANDAMET products when they were re-evaluated in 2008.

Conclusion:
Given all these arguments, the Committee considers that the actual benefit of AVANDIA and AVANDAMET products is now insufficient for it to be paid for by National Health Insurance, in comparison with existing therapies.

5.2. Improvement in actual benefit (IAB)

Not applicable

[29] Management of diabetes: Type 2 diabetes. Doctor's Guide - Chronic Condition, HAS - May 2006.
[30] D. M. Nathan et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care, volume 31, number 12, December 2008

5.3. Therapeutic use
Not applicable (see section 5.1.)

5.4. Target Population
Not applicable

5.5. Transparency Committee recommendations
The Transparency Committee recommends not maintain inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for use by hospitals and various public services.

The Transparency Committee notes once again that it has taken responsibility, in line with article R.163-21 of the Social Security Code, for re-assessment of AVANDIA and AVANDAMET products, independently of the outcome of suspension of marketing authorisation by the European and French registration authorities, and regardless of whether or not this suspension is lifted in future.

APPENDIX

OPINION OF
PUBLIC HEALTH BENEFIT AND POST-MARKETING STUDIES GROUPS
CONCERNING FINAL RESULTS (September 2010)
OF THE POST-MARKETING STUDY OF AVANDIA®/AVANDAMET®

PROTOCOL: AVANCE study: Study of usage, efficacy and tolerance of rosiglitazone (Avandia®, Avandamet®)
VERSION: Final report (September 2010)
PRODUCT: Avandia®, Avandamet®
APPLICANT: GlaxoSmithKline
DATE OF OPINION: 30/09/2010

1. Summary of background and request for study

CEPS made the first request for a post-marketing study of Actos® and Avandia® in 2002. Subsequently, because of the morbidity and mortality study requested by EMEA, the initial request was amended by the Transparency Committee in 2004, and the wording was changed to the following: "The Committee requests that an observational study be set up, to involve a dual cohort of patients receiving monotherapy and dual therapy, with long-term follow-up over not less than 2 years. This study should enable a description of patients who are treated in real-life conditions: observation of efficacy in terms of HbA1c, number of responders, treatment failure rates, and tolerance and compliance data. The Committee would like to be informed about the results of the ongoing morbidity and mortality study that was requested by EMEA."
CEPS repeated this request in its agreements of 20 and 21/09/2004, also including Avandamet®: "The applicant Takeda/GSK, along with other companies that market glitazones, shall make a commitment to fund and carry out a programme of post-marketing assessment for the Actos/Avandia/Avandamet range of products. This programme, which shall last a minimum of 2 years, shall consist of a prospective observational study of real usage conditions in terms of the profile of treated patients, adherence to the SPC, compliance, tolerance and glycaemic control (responder or non-responder, using the ANAES definitions) as well as measurement of rates of switch to insulin."

2. Remarks on the methodology used

In order to meet this request, the company set up a prospective study over 2 years, involving patients with type 2 diabetes who were starting treatment with rosiglitazone and who were followed up by general practitioners or specialists (endocrinologists or internal medicine specialists), the aim of which was to evaluate the efficacy of rosiglitazone, the profile of treated patients, adherence to the SPC, compliance and tolerance. The primary endpoints were the percentage of patients who responded to treatment (HbA1c $\leq$ 8% and/or reduction

in HbA1c ≥ 0.7 points), rates of switch to insulin (based on physician decision) and the frequency of adverse effects that led to change to or cessation of treatment.

The protocol for this study was validated in March 2005 and the study ran from 01/02/2006 (date of first patient enrolment) to 07/09/2009 (date of last patient follow-up).

The main methodological features were as follows:

- The number of centres that participated in the study is lower than that planned for in the protocol: 191 general practitioners (vs 325 planned) and 107 endocrinology or internal medicine specialists (vs 217 planned) were involved.
- In terms of patient numbers, 1120 were enrolled (1300 planned for in the protocol) and 23 were ruled out as they did not meet the inclusion criteria. 1097 patients were therefore used for the analysis.

The representativeness of the doctors was studied, by comparing the profile of investigators in the AVANCE study with that of French doctors in general: age, sex and regional distributions of generalist physician investigators were similar to those of French general practitioners as a whole. Among the specialist investigators in the AVANCE study, there was a slight under-representation of specialists who only practice in hospitals and of doctors aged over 55.

The profile of enrolled patients was compared to that of patients who met the inclusion criteria, were eligible for inclusion in this study, and were contained in the non-inclusion register: patients enrolled by general practitioners were slightly younger than those who were not enrolled (62.5 versus 60.6 years, p=0.001). These patients had been diagnosed with diabetes a little more recently and they were a little more likely to be treated with Avandamet®. No differences were observed between the two populations (enrolled and not enrolled) for patients recruited by specialists.
Of the 1,097 patients who were enrolled, 832 (76%) were followed up until the last follow-up visit and 663 (60%) were followed up for at least 24 months. The difference between these figures (832 and 663) arises from the fact that for 169 patients, the last follow-up visit took place less than 24 months after the inclusion visit. These percentages correspond to the rates of patients lost to follow-up that were planned for in the study protocol (30% over 2 years).

Analysis of the enrolment questionnaire was carried out in order to compare characteristics at the time of inclusion of patients who were followed up for at least 24 months with those followed up for less than 24 months. No significant difference was noted between the two patient groups in terms of the criteria studied, with the exception of a slight difference in age and time since disease onset.

In general, doctors and patients involved in this study were acceptably representative.
In addition, on-site quality control was carried out for approximately 5% of investigators who enrolled at least one patient (14 doctors vs 15 planned for at the start, who enrolled 54 patients of whom it was possible to audit 44 patient records). The most frequently corrected variable was date performed and HbA1c level in the inclusion questionnaire. In 2 cases, the doctor had not declared SAEs to the department of pharmacovigilance (these were declared

on the day of the audit). In summary, the quality of the data collected during the AVANCE study can be considered to be good.

3. Main results

In total, 191 general practitioners and 107 specialists (endocrinologists and internal medicine specialists) enrolled 1120 patients, of whom 23 were excluded from the analysis because they did not meet the inclusion criteria[31]. 1097 patients were used for data analysis.

3.1. Baseline patient characteristics

Of the 1097 patients used for analysis, 670 (61.1%) were enrolled when they started Avandamet® treatment and 427 (38.9%) when they started Avandia® treatment.
Of these patients, 1009, (91.8%) had at least one follow-up appointment and 988 (97.9% of the 1009) were followed up for at least 6 months, 935 (92.7%) for at least 12 months, 879 (87.1%) for at least 18 months and 663 (62.4%) for at least 24 months.

The majority of enrolled patients were men (57%), and the mean age was 61 years. The mean time since diabetes diagnosis was 7.5 years. Follow-up was mixed (provided jointly by a general practitioner and a specialist) in almost half of all cases (48.7%).
42.6% of enrolled patients were obese (BMI ≥ 30) and 43.8% were overweight. In addition, 11.6% of patients had a history of smoking (of whom 25.5% were former smokers) and rates of hypertension at the inclusion visit were 31.4% (systolic > 140 and diastolic > 80) to 54.6% (systolic > 130 and diastolic > 80).
Adherence to diet was in most cases judged to be "average" (50.4% of patients) or "poor" (29.2%) and physical activity levels were mostly light at <30 mins/day (60.1%) or moderate at 30 mins-1 hour/day (29.8%).
At inclusion, HbA1c levels from prior to the inclusion visit were available for 95.6% of patients, and mean levels were 8.0% (+/- 1.45) and median levels 7.8%. 50% of patients therefore had HbA1c of between 6.5% and 8%, and 40% had HbA1c of > 8%.

Lipid profile results were available at the time of inclusion for at least almost 80% of cases. The observed results were as follows:
- Total cholesterol: mean 2 (+/- 0.42) g/L;
- LDL cholesterol: mean 1.16 (+/- 0.35) g/L - one third of patients had a level of ≥ 1.3 g/L;
- HDL cholesterol: mean 0.49 (+/- 0.13) g/L for men and 0.55 (+/- 0.15) g/L for women;
- Triglyceride: mean 1.71 (+/- 1.19) g/L (median 1.42 g/L) - 47.5% of patients had a level of ≥ 1.5 g/L.

Of the 931 patients for whom information was available (84.9%), 12.4% had renal failure, defined as creatinine clearance of less than 60 mL/minute. Just one patient had creatinine clearance of between 15 and 30 mL/minute and no patients had creatinine clearance of less than 15 mL/minute.
Cardiovascular involvement was reported in 26% of enrolled patients: Hypertension (9.8% of all patients), coronary artery disease (7.3%), cardiac failure (3.2%, 35 patients), lower limb arterial disease (2.6%), carotid artery stenosis (1.6%) and 4 cases (0.4%) of heart valve

[31] Three inclusion criteria were used: 1. patient with type 2 diabetes consulting spontaneously; 2. patient starting or started within the last month on Avandia or Avandamet treatment; 3. patient who had given oral consent.

disease. The other comorbidities that were most commonly reported at the time of inclusion were neurological involvement (8.6% of patients, more than half of whom had diabetic neuropathy), ophthalmological involvement (7.8%, with most cases being diabetic retinopathy) and stroke in 3.1% of cases.

The most commonly reported reasons for prescribing rosiglitazone were failure of oral monotherapy (53.8% of patients), patient weight (24.1%), treatment failure other than failure of oral monotherapy (23.4%), intolerance or contraindication of metformin (19%).
Antidiabetic treatment including rosiglitazone prescribed at the inclusion visit was dual oral therapy (51.9% of cases), triple therapy (29.6%), monotherapy (16.4%) and, in rare cases, quadruple therapy or treatment including insulin (2.0%).
The most commonly prescribed daily dose (of both Avandia® and Avandamet®) was 4 mg (59.8%). Just one patient was prescribed a daily dose of Avandia® that was greater than 8 mg.
At the time of inclusion, 79.2% of the patients were receiving treatment for cardiovascular disease. In most cases these were lipid-lowering medications (55.4%), renin-angiotensin system medication (48.5%), beta-blockers (21.1%), calcium channel blockers (15.2%) or diuretics (11.4%).

3.2. Adherence to indications and contraindications

Of the 1097 patients analysed, indications, according to guidelines for use of antidiabetics that were in use at the time, were not respected in 30.1% of cases, involving:

- 116 patients receiving dual therapy (10.6%)
- 83 patients receiving triple therapy (7.6%)
- 117 patients receiving monotherapy (10.7%)
- 17 patients receiving quadruple therapy (1.5%)
- In addition, 6 patients were receiving insulin (0.5%).

Only the most significant contraindications were analysed: the need to carry out liver function tests before first prescribing the drugs, liver failure, cardiac failure and renal involvement for Avandamet.
Liver function tests were available before prescription of rosiglitazone for 60.5% of patients, and transaminase levels of > 2.5 times the upper limit of normal was found in 1.7% (AST) and 1.8% of patients (ALT).
154 patients receiving Avandamet® were noted to have renal failure (creatinine clearance < 70 mL/minute) (14.0% of the 1097 patients who were included). In these patients, clearance was between 50-70 mL/minute inclusive in 10.4% of cases and between 30-50 mL/minute in 89.6% of cases.
3.2% of patients enrolled were noted to have cardiac failure (n=35), and this was more common in patients enrolled by general practitioners (4.7%) than for those enrolled by specialists (0.9%). Most of these cases of cardiac failure were stage 1 (37.5%) or 2 (53.1%); only 3 had stage 3 heart failure (9.4%) and none had stage 4.

Serious misuse, corresponding to prescription of the drug despite the presence of liver cytolysis with increased AST and ALT (> 2.5 times the upper limit of normal) or cardiac failure, was reported in 1.7%, 1.8% and 3.2% of patients respectively.
Taking all causes of misuse into account, including failure to measure transaminase levels, the proportion of patients involved is 52.1% (572 patients of the 1097 analysed).

3.3. Patient progress

- For patients enrolled by general practitioners:

The mean HbA1c level at time of inclusion was 8.3%, and the median level was 7.8%. This level reduced by 18 months after start of treatment to around 6.95% and subsequently increased and stabilised at around 7.2% after 24-30 months.
The proportion of patients with HbA1c of < 7% was 18.4% at time of inclusion and increased subsequently, reaching 60.3% after 18-24 months, followed by another reduction to 50.7% after 24-30 months.
The proportion of patients with HbA1c of ≤ 8% was 60.2% at time of inclusion and increased subsequently, reaching 89.4% after 18-24 months, followed by another reduction to 76.9% after 24-30 months.
The proportion of patients whose HbA1c reduced by at least 0.7 points during the follow-up period was around 50% after 24-30 months.
The proportion of patients meeting the 2 criteria "HbA1c ≤ 8%" and/or reduction in HbA1c by at least 0.7 points was around 80**%** after 24-30 months.

- For patients enrolled by specialists:

The mean HbA1c level at time of inclusion was 8.02%, and the median level was 7.8%. This level reduced by 18 months after start of treatment to around 7.1% and subsequently increased and stabilised at around 7.2% after 24-30 months.
The proportion of patients with HbA1c of < 7% was around 18% at time of inclusion and increased subsequently, reaching 53.7% after 18-24 months, followed by another reduction to 49.1% after 24-30 months.
The proportion of patients with HbA1c of ≤ 8% was 58.5% at time of inclusion and increased subsequently, reaching 87.3% after 24-30 months.
The proportion of patients whose HbA1c reduced by at least 0.7 points during the follow-up period was around 51.8% after 24-30 months.
The proportion of patients meeting the 2 criteria "HbA1c ≤ 8%" and/or reduction in HbA1c by at least 0.7 points was around 91.8**%** after 24-30 months.

A mixed model was used to analyse changes in HbA1c: following initiation of rosiglitazone treatment, a clear reduction in HbA1c was observed over less than 6 months (initial levels being 8.0%), and this level then stabilised at around 7-7.2%.

At the time of initial rosiglitazone prescription, 0.4% of patients were receiving insulin treatment. During follow-up, insulin treatment was started for 9.7% of patients; this was more common in patients enrolled by specialists (15.3%) than in those enrolled by general practitioners (6.1%). Treatment switch (stopping rosiglitazone and prescription of insulin on the same date) was observed for 6.1% of patients (10.3% of those seen by specialists and 3.4% of those seen by general practitioners).

A moderate increase in weight was observed at 2 years for patients treated with rosiglitazone, particularly patients enrolled by specialists (around 2 kg on average, vs 1.4 kg for patients enrolled by general practitioners, 24-30 months after starting rosiglitazone treatment). A mixed model was used to study changes in weight over 2 years: an increase of around 500 grams was observed in a little less than one year, followed by a slight decrease and then stabilisation.

A slight improvement in lipid levels was observed over the follow-up period: a reduction in total cholesterol (from 2 g/L on inclusion to 1.90 g/L at the last follow-up visit), triglycerides (from 1.7 to 1.5 g/L) and LDL cholesterol (1.16 to 1.08 g/L) accompanied by a stabilisation in HDL cholesterol (at around 0.50 g/L).

Rates of maintenance of patients on rosiglitazone reduced steadily over time, and instances of cessation of treatment were evenly distributed throughout the follow-up period.
At one year, 84.1% of patients were still receiving rosiglitazone and at 24 months this figure was 70.3%: 59% of patients enrolled by specialists and 83.9% of those enrolled by general practitioners.

In general, patients enrolled by specialists underwent more changes to their treatment than those enrolled by general practitioners. For example, of the 357 patients enrolled by general practitioners and who were receiving dual therapy at the time of inclusion, with rosiglitazone, 79.6% were still receiving dual therapy at the end of the follow-up period (vs 65.1% of patients enrolled by specialists), 10.1% had changed to triple therapy (vs 13.6%), 4.2% had switched to insulin treatment (with or without an oral antidiabetic agent) (vs 6.5%) and 6.2% (vs 13.0%) had switched to monotherapy.

3.4. Tolerance

Of the 1120 patients included in this study**,** 1034 were included in the tolerance population[32].
Spontaneous notifications involved a total of 54 patients (5.2% of the tolerance population) and all notifications (spontaneous + "solicited") involved a total of 148 patients (14.3% of the tolerance population). Of all notifications made, 11.5% (119) led to cessation of treatment or dose reduction and 4.9% (51) were serious AEs.
Overall analysis of notifications showed that the nature and frequency of AEs in this group were similar to those seen in the group of spontaneous AEs. The most commonly notified effects were: weight gain (3%), peripheral oedema (2.5%), cardiac conditions (2.3%, 1.9% being cardiac failure), gastrointestinal problems such as diarrhoea (1.5%) and nausea (1.0%), in most cases linked to metformin given in combination with Avandia® or contained in Avandamet, dyspnoea (1.6%). The risk of experiencing an AE was greater during the first months of treatment. Multivariate analysis enabled identification of 3 variables that were significantly correlated with declaration of an AE:

- Patients who had a cardiovascular complication or disease on inclusion (OR = 2.3 (95% CI = [1.5; 3.5]))
- Patients who had an ophthalmological complication or disease on inclusion (OR = 1.9 (95% CI = [1.0; 3.6]))
- Those who had been enrolled by a specialist (OR = 1.95 (95% CI = [1.3; 2.9])).

In total, 46 serious non-fatal AEs and 5 deaths were recorded. These deaths were reported as reasons for leaving the study in the patient record, but were not declared as AEs by the

[32] Analysis of overall safety was done first using only those AEs that were declared spontaneously by investigators (spontaneous notifications), and then taking into account those AEs that were investigated following analysis of patient records and for which information had been sought by GSK ("solicited" notifications).

investigators. GSK requested documentation for all these deaths. The causes of death were as follows:

- cardiac failure in a woman aged 81 years with a history of hypertension and MI with quadruple coronary artery bypass and who had started on Avandia® treatment (20 months previously) when she had grade III cardiac failure associated with renal failure;
- cardiac arrest in a woman aged 85 years, who had been receiving Avandia® treatment for 3.5 months, who had hypertension and hyperlipidaemia, who probably (given her anticoagulant and anti-arrhythmia treatment) had heart disease with embolic cause;
- alcoholic cirrhosis complicated by liver failure in a man aged 66 years;
- two deaths of unknown aetiology, in patients receiving triple therapy for diabetes, the first in a woman aged 90 years with a history of hypertension, hyperlipidaemia, renal artery stenosis and lower limb artery disease and the second in a man aged 64 years with a history of smoking, hypertension, hyperlipidaemia and who had carotid artery stenosis.

The most common SAEs were cardiac: these affected 26 patients (2.4% of the tolerance population): 22 patients presented with cardiac failure or acute pulmonary oedema or a reduction in left ventricular ejection fraction, and 8 had ischaemic cardiac events: 3 cases of MI, 1 case of unstable angina, 3 cases of coronary artery disease, 1 case of coronary artery stenosis (3 other cases of coronary artery stenosis and one repeat intra-stent stenosis were diagnosed in addition in some patients who experienced ischaemic events).
The median time to occurrence of these events was 12.5 months for ischaemic events and 15 months for cardiac failure.

No cases of fracture were notified.

3.5. Compliance

Compliance with rosiglitazone treatment (regardless of date of follow-up) was considered to be "full" for 85% to 91% of patients, depending on investigator, and 80% to 89% depending on patient profile. These proportions are similar to those reported by patients on other antidiabetic agents (between 80% and 88%).
Following multivariate regressions, 2 variables were found to be significantly correlated with compliance:

- Patients who showed good compliance with lifestyle and diet advice (in comparison with those who showed average or poor compliance) were more likely to be compliant (OR = 3.7 (95% CI = [1.8; 7.6]));
- Patients receiving a daily dose of more than 4 mg on inclusion were more likely to be compliant than those receiving a dose that was less than or equal to 4 mg (OR = 2.6 (95% CI = [1.1; 6.5])).

4. Discussion

For 69.1% of patients in the AVANCE study, the indications contained in the SPCs for Avandia® and Avandamet® and in therapeutic management guidelines for diabetes were adhered to. Most cases of rosiglitazone misuse were linked to a failure to measure transaminase levels and to failure to respect guidelines for use of the product. Serious misuse (failure to adhere to contraindications such as cardiac failure and liver cytolysis) was identified in 6.7% of patients.

In the AVANCE study, the reduction in HbA1c was between -0.8 and -1.0 points depending on time to follow-up and the specialism of the investigator, and the rate of patients who responded to treatment after a full 24 months of follow-up increased to around 50%, and the proportion of patients whose HbA1c levels had reduced by at least 0.7 points was around 43-60%, varying by time to follow-up and the specialism of the investigator. These results are in line with those seen in the clinical trials.

In the AVANCE study, the mean weight of patients enrolled by specialists was 84.5kg at the time of inclusion, and this increased by around 1 kg over a little more than 24 months. Results observed for patients enrolled by general practitioners showed a variability over time that was more difficult to interpret.

A tolerance analysis was done using 2 approaches: the first was limited to analysis of spontaneous notifications of AEs, as initially provided for in the protocol (54 patients affected, i.e. 5.2% of the patients in the tolerance population), and the second was a more active approach to counting AEs, which was adopted because of the lack of spontaneous notification of events that were observed in patient records and that would have been expected with rosiglitazone (148 patients affected, or 14.3%).

Apart from gastro-intestinal effects (which are linked not to rosiglitazone but to the metformin that is contained in Avandamet®), the most common effects were the known effects of glitazones: peripheral oedema, weight gain, cardiac failure, dyspnoea associated with weight gain or sign/symptom of cardiac failure, headaches, myalgia, dizziness and anaemia.

Cardiac failure was reported for 26 patients in total, i.e. 2.5% of the cohort. The mean age of these patients was higher than for the cohort as a whole, and these patients had factors that predisposed them to cardiac failure. Of the 26 cases of cardiac failure, 14 (1.3% of the patients in the cohort) met one criterion for severity.

Cardiac failure is a known effect of glitazones: in the ADOPT clinical study[33] involving patients treated with a monotherapy, the OR for rosiglitazone was 1.22 (vs metformin) and 2.20 (vs glibenclamide), in the RECORD study[34] involving patients with type 2 diabetes treated with rosiglitazone as an add-on to metformin or a sulfonylurea, the OR was 2.10 (95% CI = 1.35;3.27) (vs metformin or a sulfonylurea) and, in the PROactive study[4] involving patients with type 2 diabetes and high levels of cardiovascular risk, the OR was 1.43 (vs placebo). The results of the AVANCE study are in line with those of the ADOPT and RECORD studies (in which the incidence of cardiac failure in those receiving rosiglitazone was 1.5% and 2.7% respectively).

Eight patients (0.8% of the tolerance population) developed non-fatal ischaemic cardiac events during the study. All these patients had at least one cardiovascular risk factor apart from diabetes. These results are in line with the AVANTAGE study[1], in which ischaemic cardiac events were notified for 0.2% of patients who were followed up at 1 year.

At 24 months, 70.3% (95% CI = [67.3%; 73.3%]) of patients were still being treated with rosiglitazone, which is in line with the efficacy and tolerance of the product.

Compliance with rosiglitazone treatment was considered to be full for 85-91% of patients, depending on investigator, and 80-89% depending on patient profile.

[33] Kahn SE et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. NEJM 2006;355:2427-43.

[34] Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJV, for the RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009 DOI: 10.1016/S0140-6736(09)60953-3.

5. Conclusion

This study was properly conducted, under actual usage conditions, and provides answers to the questions asked by CEPS and the Transparency Committee.

Given the sample size and length of follow-up, it shows no discrepancy with respect to existing data on efficacy, maintenance, compliance or tolerance.

It was observed that there were differences with respect to the 2006 guidelines for the use of antidiabetic agents in 30.9% of cases: serious violations of contraindications (liver cytolysis and cardiac failure) were observed in 3.2% and 3.5% of cases respectively.