HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

20 July 2011

ACTOS 15 mg, tablets
B/28 (CIP code: 355 632-4)
B/50 (CIP code: 355 633-0)
B/84 (CIP code: 371 688-0)

ACTOS 30 mg, tablets
B/28 (CIP code: 355 635-3)
B/50 (CIP code: 355 637-6)
B/84 (CIP code: 371 691-1)

Applicant: TAKEDA

pioglitazone
ATC code: A10BG03
List I

Date of the initial Marketing Authorisation (centralised procedure): 13 October 2000, final corrected version dated 31 August 2010

Reason for the review: Reassessment of actual benefit (AB) in compliance with article R 163-21 of the French Social Security Code.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

pioglitazone hydrochloride

1.2. Indications

“Pioglitazone is indicated in the treatment of patients with type 2 diabetes mellitus:
as monotherapy:

- in adults, especially in overweight cases, inadequately controlled by diet or physical exercise and in whom metformin is contraindicated or not tolerated.

As dual oral therapy in combination with:

- metformin in adults, especially if overweight, when a maximal tolerated dose of an oral monotherapy with metformin does not allow sufficient glycaemic control to be achieved;
- a sulphonylurea, exceptionally in adults intolerant to metformin or for whom metformin is contraindicated, when the maximal tolerated dose of an oral monotherapy with hypoglycaemic sulphonylurea does not allow sufficient glycaemic control to be achieved.

As triple oral therapy, in combination with :

- metformin and a sulphonylurea in adults, especially if overweight, in whom the above dual therapy combinations do not allow sufficient glycaemic control to be achieved.

Pioglitazone is also indicated in combination with insulin in type 2 diabetes mellitus patients insufficiently controlled with insulin and in whom metformin is contraindicated or poorly tolerated.”

1.3. Dosage

“Treatment with pioglitazone may be initiated at a dose of 15 mg or 30 mg in a single daily intake. The dose may be gradually increased up to 45 mg in a single daily intake.
In combination with insulin, the insulin dose can be maintained when introducing the pioglitazone treatment. In the event of hypoglycaemia, the insulin dose will need to be decreased.

Special population
Elderly patients
No dose adjustment is necessary in elderly subjects (see section 5.2 of the SPC).

Renal impairment
No dose adjustment is necessary in patients suffering from renal impairment (creatinine clearance > 4 ml/min) (see section 5.2 of the SPC). Pioglitazone should not be administered in dialysed patients, as no information is available relating to this population.

Hepatic impairment
Pioglitazone should not be used in patients suffering from hepatic impairment (see section 4.3 and 4.4 of the SPC)

Paediatric population
The safety and efficacy of ACTOS in children and adolescents under the age of 18 years have not been established. No data are available.

Method of administration

Pioglitazone is administered orally in a single daily dose during or outside mealtimes. The tablets should be swallowed with a glass of water."

1.4. Contraindications

"Pioglitazone is contraindicated in patients with:
- hypersensitivity to the active ingredient or to one of the excipients,
- cardiac failure or history of cardiac failure (NYHA class I to IV)
- hepatic impairment,
- diabetic ketoacidosis."

1.5. Special warnings and precautions for use (cf. SPC)

"Fluid retention and cardiac failure
Pioglitazone can cause fluid retention, which is liable to aggravate or accelerate the development of heart failure. In patients exhibiting at least one risk factor for developing heart failure (e.g. history of myocardial infarction, symptomatic coronary artery disease), doctors should start pioglitazone at the lowest available dose and gradually increase it.
It is advisable to look for the signs and symptoms of heart failure, weight gain or oedema, especially in patients with a reduced cardiac reserve. Post-marketing cases of heart failure have been observed when insulin was combined with pioglitazone in patients with a history of heart failure. When pioglitazone is used in combination with insulin, patients should be monitored for the appearance of signs or symptoms of heart failure, weight gain and oedema. Since insulin and pioglitazone are associated with fluid retention, their concomitant administration can increase the risk of oedema. Pioglitazone should be discontinued if there is any deterioration of the cardiac status.
A cardiovascular morbidity/mortality study with pioglitazone has been carried out in type 2 diabetes mellitus patients under 75 years of age with a pre-existing major macrovascular disease. Pioglitazone or a placebo were added to pre-existing antidiabetic and cardiovascular treatments for a duration of up to 3.5 years. This study showed an increase in reported cases of heart failure, but without any increase in the mortality. Given the limited experience in patients aged over 75 years in this study, special attention should be paid to these patients."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

A: Alimentary tract and metabolism
A10: Drugs used in diabetes
A10B: Blood glucose lowering drugs, excluding insulins
A10BG: Thiazolinediones
A10BG03: Pioglitazone

2.2. Medicines in the same therapeutic category

Comparator medicines:
Rosiglitazone (AVANDIA) and the fixed rosiglitazone / metformin combination (AVANDAMET), another compound in the glitazone family, whose MA has been suspended since 3 December 2010 and whose actual benefit (AB) was regarded by the transparency Committee to be insufficient to justify its reimbursement by public funds when compared to existing therapies in its Opinion of 3 November 2010.

The COMPETACT fixed combination (pioglitazone hydrochloride / metformin hydrochloride) indicated in the treatment of type 2 diabetics, especially in cases of overweight, which is inadequately balanced with metformin alone at the maximum tolerated dose. The Committee took the view that COMPETACT's actual benefit was insufficient to justify its reimbursement by public funds when compared with existing therapies in its Opinion of 25 May 2011.

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 alphaglucosidase inhibitors,
  - sulfonylureas,
  - glinides,
  - dipeptidyl peptidase-4 (DPP4) inhibitors; *sitagliptin-based proprietary medicinal products have been granted an indication as monotherapy but have not yet been assessed by the Committee*

- as dual oral therapy:
  - in patients with type 2 diabetes who have not achieved adequate glycaemic control despite maximal tolerated doses of oral monotherapy with metformin:
    - sulfonylureas
    - intestinal alpha-glucosidase inhibitors
    - glinide
    - DPP-4 inhibitors (gliptins)
    - parenteral incretin mimetics

  - in type 2 diabetic patients with inadequate glycaemic control despite maximum tolerated doses of oral sulfonylurea monotherapy, who show intolerance to metformin or for whom metformin is contraindicated:
    - intestinal alphaglucosidase inhibitors
    - DPP-4 inhibitors (gliptins)
    - parenteral incretin mimetics (in combination with a sulfonylurea)

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

- in combination with insulin in the event of contraindication or intolerance to metformin in type 2 diabetics:
  - sulfonylureas
  - intestinal alpha-glucosidase inhibitors

3 REMINDER OF PREVIOUS TRANSPARENCY COMMITTEE OPINIONS

Opinion of 28 March 2001

ACTOS 15 mg and 30 mg tablets (boxes of 28 and 50): 1st registration
- in combination with metformin, only in obese patients
- in combination with a sulfonylurea, only in patients intolerant to metformin or for whom metformin is contraindicated

(box of 28 National Health Insurance and Hospitals, box of 50 Hospitals)

Actual benefit
In combination with an oral antidiabetic, the efficacy/adverse effects ratio of this proprietary medicinal product is favourable and seems, based on the available data, to be substantial.
The actual benefit of ACTOS in the current indications is substantial.

Improvement in actual benefit
According to currently available data and in particular in the absence of any 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.

Opinion of 7 May 2003

ACTOS 15 mg and 30 mg tablet (boxes of 28 and 50):
- lifting of the restrictions allowing only specialists to prescribe.

Opinion of 24 March 2004

ACTOS 15 and 30 mg tablets (boxes of 28):
- reassessment of the improvement in actual benefit (IAB) in the indication in combination,
- change in the conditions of registration following changes to the SPC: extension of the monotherapy indication + possibility of increasing the dosage to 45 mg/day + modification of the indication in combination with metformin

ACTOS 45 mg (boxes of 28): registration for National Health Insurance and Hospitals.

Actual benefit
The efficacy/adverse effects ratio for this proprietary medicinal product is, as things stand at the moment, high.
The actual benefit of ACTOS is substantial.

Improvement in actual benefit
As monotherapy, ACTOS offers a (minor) level IV improvement in actual benefit compared to gliclazide.
In combination with metformin, ACTOS offers a (minor) level IV improvement in actual benefit compared to the gliclazide + metformin combination.
In combination with a sulfonylurea, ACTOS does not offer any improvement in actual benefit (level V) in comparison with the metformin + sulfonylurea combination.

Transparency Committee recommendations
The committee wishes to give a favourable opinion on lifting the exception drug status of ACTOS.
The Committee would like an observational study to 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 EMA.
Note: ACTOS 45 mg not registered

Opinion of 2 April 2008

- Reassessment of the improvements in the actual benefit (IAB) in the indications as monotherapy and as oral dual therapy (in combination with metformin or sulfonylurea) following the submission of new data.

Actual benefit
The efficacy/adverse effects ratio for the proprietary medicinal product ACTOS is moderate, in the absence of a demonstrable benefit in terms of morbidity and mortality and a less than favourable tolerance profile, as confirmed by recent data (peripheral oedema, macular oedema, heart failure without any increase in mortality, weight gain, fracture risk in women).
The Committee considers that the actual benefit of ACTOS remains substantial based on current knowledge.

Improvement in actual benefit
Given the new efficacy and tolerability data, ACTOS does not provide any improvement in actual benefit in the management of patients with type 2 diabetes treated by monotherapy or oral dual therapy, in comparison with the currently available oral antidiabetics.

- Registration for National Health Insurance and Hospitals as triple oral therapy and in combination with insulin.

As triple oral therapy
The efficacy/adverse effects ratio for this proprietary medicinal product in its extension of the indication as triple oral therapy is moderate according to currently available data.
The actual benefit of ACTOS in its indication as triple oral therapy is substantial.

ACTOS, 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.

In combination with insulin, in the event of a contraindication or intolerance to metformin

According to available data, the efficacy/adverse effects ratio for this proprietary medicinal product in its extension of the indication in combination with insulin is moderate.
In its indication in combination with insulin, taking account of its modest quantitative effect, scarcely favourable tolerance profile of the insulin + pioglitazone combination (including weight gain and increased incidence of heart failure), and the existence of effective drug alternatives, the transparency Committee regards the actual benefit of ACTOS as moderate.

ACTOS, in combination with insulin in the event of a contraindication or intolerance to metmorfin, does not offer any improvement in actual benefit (IAB) (level V) in the management of type 2 diabetes.

Opinion of 28 May 2008

Registration for National Health Insurance and Hospitals in packs of 30 tablets to a box in addition to the presentations in boxes of 28.
Note: presentations not registered

Opinion of 23 September 2009

Registration for National Health Insurance and Hospitals in packs of 84 tablets to a box

4 ANALYSIS OF DATA MADE AVAILABLE SINCE PREVIOUS OPINION

4.1. Efficacy

Within the framework of this reassessment, the company provided studies already assessed by the Committee as well as studies carried out subsequent to the latest opinions of the transparency Committee relating to the biotherapy indication.
Of the new data submitted,[1, 2, 3, 4, 5, 6, 7, 8] none will be presented in this document, either because they did not involve an assessment specifically of pioglitazone, or they assessed pioglitazone in situations not covered by the MA, or else their methodology was questionable (assessment based on an intermediate criterion, it was an open study, the analysis was post hoc, multiplicity of non-prioritised endpoints, etc.).
Moreover, some were already available at the time of previous Committee assessments.[9, 10, 11, 12]

No other studies with a sufficient level of proof assessing ACTOS were found in the literature.

[1] Bolli G, Dotta F, Colin L et al. Comparison of vildagliptin and pioglitazone with type 2 diabetes inadequately controlled with metformin. Diabetes, Obesity and Metabolism 2009; 11: 589-595.
[2] Derosa G, Maffioli P, Ferrari I, Mereu R, Ragonesi PD, Querci F, Franzetti GI, Gadaleta G, Ciccarelli L, Piccinni MN, D'Angelo A, Salvadeo SAT. Effects of One Year Treatment of Vildagliptin Added to Pioglitazone or Glimepiride in Poor Controlled Type 2 Diabetic Patients. Horm Metab Res 2010; 42: 663-669.
[3] Derosa G, Maffioli P, Salvadeo SAT, Ferrari I, Ragonesi P, Querci F, Franzetti I, Gadaleta G, Ciccarelli L, Piccinni N, D'Angelo A, Cicero AFG. Direct comparison among oral hypoglycaemic agents and their association with insulin resistance evaluated by euglycemic hyperinsulinemic clamp: the 60's study. Metabolism Clinical and Experimental 2009; 58: 1059–1066.
[4] Derosa G, Maffioli P, Salvadeo SAT, Ferrari I, Ragonesi P, Querci F, Franzetti I, Gadaleta G, Ciccarelli L, Piccinni N, D'Angelo A, Cicero AFG. Direct comparison among oral hypoglycaemic agents and their association with insulin resistance evaluated by euglycemic hyperinsulinemic clamp: the 60's study. Metabolism Clinical and Experimental 2009; 58: 1059–1066.
[5] Scheen AJ, Tan MH, Betteridge DJ, Birkeland K, Schmitz O, Charbonnel B; PROactive investigators. Diabet Med. 2009; 12: 1242-9.
[6] Yoon KH, Shockey GR, Teng R, Golm GT, Thakkar PR, Meehan AG, Williams-Herman DE, Kaufman KD, Amatruda JM, Steinberg H. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and pioglitazone on glycemic control and measures of β-cell function in patients with type 2 diabetes. Int J Clin Pract. 2011; 65:154-64. doi: 10.1111/j.1742-1241.2010.02589.x.
[7] Karamanos B, Thanopoulou A, Drossinos V, Charalampidou E, Sourmeli S, Archimandritis A; Hellenic ECLA Study Group. Study comparing the effect of pioglitazone in combination with either metformin or sulphonylureas on lipid profile and glycaemic control in patients with type 2 diabetes (ECLA). Curr Med Res Opin. 2011; 27: 303-13. Epub 2010 Dec 9.
[8] Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes. The PERISCOPE randomized controlled trial. JAMA 2008; 299: 1561-1573.
[9] Jochen Seufert, Richard Urquhart P. 2- Year effects of Pioglitazone add-on to sulfonylurea or metformin on oral glucose tolerance in patients with Type 2 Diabetes. Diabetes Research and clinical pratice 2008; 79: 453-460.
[10] Charpentier G, Halimi S, F-PIO-100 study investigators. Earlier triple therapy with pioglitazone in patients with type II diabetes. Diabetes, Obesity and Metabolism. Volume 11, issue 9, pages 844-854, September 2009.
[11] Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK et al. Secondary prevention of macrovascular events in patients with type 2 diabetes: a randomized trial of pioglitazone. The PROactive Study (PROspective pioglitazone Clinical Trial in macrovascular Events). Lancet 2005; 366: 1279–1289.
[12] Wilcox R, Kupfer S, Erdman E et al. PROactive 10: Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type 2 diabetes: results from PROspective pioglitazone Clinical Trial in macroVascular Events. Am. Heart J. 2008; 155: 712-717.

4.2. Adverse effects data

4.2.1. Data stemming from PSURs

On the basis of the postmarketing pharmacovigilance data on the ACTOS proprietary medicinal products which emerged from the last eight Periodic Safety Update Reports covering the period from 1 February 2007 to 31 July 2011, a total of 5823 adverse events were reported for 3667 cases (379 of which were serious and expected, 930 serious and unexpected, 1586 non-serious and unexpected) with an exposure of 14.2 million patient years.
Of the 71 cases with a fatal outlook, 15 report a death. In seven cases it was heart failure, in six cases a severe cirrhotic liver disorder, hepatic failure or hepatocellular lesion.

Since ACTOS proprietary medicinal products have been on the market, the following have been reported:
- 1311 cases of heart failure, including 964 serious cases,
- 1265 cases of liver damage, including 465 serious cases,
- 206 cases of cardiac ischaemia (182 serious) and 55 cases (54 serious) of cerebrovascular ischaemia,
- 193 serious cases and 1161 non-serious cases of weight gain,
- 140 cases of cancer, including 40 cases of bladder cancer,
- 114 cases, including 74 serious cases of fractures,
- 66 serious cases and 71 non-serious cases of macular oedema[13],
- 29 serious cases and 19 non-serious cases of rhabdomyolysis.

4.2.2. Data taken from the literature

Compared to sulfonylureas, pioglitazone has been associated with an increased risk of congestive heart disease (OR = 1.68, 95% CI [0.99; 2.85]).[14]
A meta-analysis[15] that included 29 trials versus placebo, assessed the risk of heart failure in patients with type 2 diabetes or at high risk of developing type 2 diabetes (n = 20,254). Glitazones have been associated with a high heart failure risk compared to placebo (OR = 1.59, 95% CI [1.34; 1.89], p < 0.00001), this risk being higher with rosiglitazone (OR = 2.73, 95% CI [1.46; 5.10], p < 0.00001) than with pioglitazone (OR = 1.51, 95% CI [1.26; 1.81], p NS].
The risk of onset of severe heart failure, compared to a placebo, was the same for each of the glitazones (OR = 1.47, 95% CI [1.16; 1.87], p = 0.002).
Glitazones have been associated with a risk of oedema (OR = 2.04, 95% CI [1.85; 2.26], p < 0.00001).

Compared to metformin, pioglitazone has been associated with an increased risk of fractures (OR = 1.57, 95% CI [1.13; 2.17]).[3]
This increased fracture risk has been observed in particular in women over the age of 65 and after 1 year of treatment.[16]

The SPC states “that an increased incidence in bone fractures in women has been observed when analysing the data from randomised, controlled, double-blind clinical trials involving

[13] The SPC states that cases of onset or exacerbation of macular oedema, with reduction of visual acuity, have been reported after marketing. Several of these cases have been associated with concomitant peripheral oedema.
[14] Oral diabetes medications for adults with type 2 diabetes. An update. Comparative effectiveness review number 27. Effective healthcare. AHRQ – Agency for Healthcare Research and Quality. March 2011.
[15] Hernandez AV et al. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. Am J Cardiovasc drugs 2011; 11: 115-28.
[16] Habib ZA et al. Thiazolidinedione use and the longitudinal risk of fractures in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 2010; 95: 592-600.

8100 patients treated with pioglitazone and over 7400 patients treated with comparator drugs followed up for up to 3.5 years. Fractures were observed in 2.6% of the women treated with pioglitazone as against 1.7% of the women treated with a comparator drug."

A new risk has been identified relating to the onset of pneumonia.[17]

Recent data from the literature point to the weight gain, oedema, fractures and the risk of congestive heart failure under treatment with pioglitazone.[18,19]

Recent data establish a potential link between pioglitazone treatment and bladder cancer.[20]
The PROactive[21,22] randomised, double-blind prospective study of morbidity/mortality over a period of 34.5 months, comparing pioglitazone with a placebo and involving 5238 patients with type 2 diabetes, has revealed 14 cases of bladder cancer in patients treated with pioglitazone (n = 2605), as against six cases in the placebo group (n = 2633).
In another study, requested by the FDA, comparing pioglitazone with glimepiride and assessing hepatic tolerability, two cases of bladder cancer were recorded under pioglitazone, as against zero cases under glimepiride. Combining the results of this study with those of the PROactive study, the odds ratio of contracting bladder cancer under pioglitazone is 2.68 (95% CI [1.05; 6.85]).
Another postmarketing study lasting 36 months requested by the FDA recorded three cases under pioglitazone (n = 1051) versus 0 cases under glibenclamide (n = 1046). Combining the results of this study with those of the PROactive study would give an odds ratio of contracting bladder cancer under pioglitazone is 2.87, 95% CI [1.08; 8.9].

The interim results at 5 years of a cohort study[23,24] conducted in the United States, whose aim was to compare the incidence of bladder cancer in patients exposed to pioglitazone versus non-exposed patients and involving 193,099 patients, of whom 30,173 were treated with pioglitazone, showed a statistically significant increase in the risk of bladder cancer in patients treated for more than 24 months (HR = 1.4, 95% CI [1.03; 2.0]).
In one study,[25] whose aim was to detect a relationship between bladder cancer and taking pioglitazone on the basis of spontaneous notifications to the FDA between 1 January 2004 and 31 December 2009, 93 cases of bladder cancer were declared, 31 of which were associated with pioglitazone (OR = 4.30, 95% CI [2.82; 6.52] p < 0.001).

On 29 March 2011, 15 cases of bladder cancer were reported in France, of which 12 were after an exposure of over 12 months.
On 31 May 2011,[26] 46 cases of bladder cancer under pioglitazone were notified in France, 42 of which during the course of 2011 (two cases had been declared prior to the FDA alert, two cases in late 2010).[27]

[17] Singh S et al. Long-term use of thiazolidinediones and the associated risk of pneumonia or lower respiratory tract infection: systematic review and meta-analysis. Thorax 2011; 66: 383-8.
[18] 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. Diabetologia. 2009; 52: 17-30.
[19] Patrick J Phillips, Stephen M Twigg. Oral hypoglycaemics: A review of the evidence. Australian family physician, Vol 39, No. 9, Sep 2010: 651-653.
[20] Philip Home, DM, DPHIL. Safety of PPAR Agonists. Diabetes care, May 2011, Volume 34. No supplement 2, S215-S219.
[21] Dormandy J et al. PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial, Lancet 2005; 366: 1279-1289.
[22] Dormandy J et al. Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. Drug Saf 2009; 32: 187-202.
[23] Ten-year observational cohort study based on an American database – KPNC (Kaiser Permanent Northern California) Study – requested in 2005.
[24] Lewis JD et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care 2011; 34: 916-22.
[25] Piccinni C, Motola D, Marchesini G, Poluzzi E. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. Diabetes care 2011. 34: 1369-1371.
[26] Review of the data available on the national pharmacovigilance database on 31 May 2011.
[27] 25/42 cases identified as urothelial carcinomas. There are no particulars about the other cases. Two cases had a fatal outcome.

A cohort study[28] was carried out based on data from SNIIRAM[29] (the French national health insurance database) linked to the data in the PMSI (programme for clinical information system). The cohort included 1,491,060 diabetic patients, beneficiaries of the French general health insurance scheme and aged between 40 and 79 years in 2006. Patients who had cancer of the bladder before admission to the cohort or in the 6 months following their entry in the cohort were excluded. Exposure to pioglitazone (and to every antidiabetic) was defined in SNIIRAM by the issue of at least two prescriptions for the active ingredient in 6 consecutive months. The follow-up covered a period of four years, from 2006 to 2009. The cases of bladder cancer were identified by the hospitalisations reported in the PMSI with a first- or second-listed diagnosis of bladder cancer and during the same period of hospitalisation a major surgical procedure or bladder instillation of a pharmacological agent by urethral catheterisation and/or chemotherapy and/or radiotherapy. The cases in question related to infiltrating bladder cancer.
A sensitivity analysis was carried out.

Results
The group exposed to pioglitazone consisted of 155,535 diabetics and the non-exposed group of 1,335,525 diabetics. The mean age of the exposed patients was 61.5 years, compared with 63.4 years for the non-exposed. There were 175 incident cases of bladder cancer in the group exposed to pioglitazone and 1841 in the non-exposed group. The use of pioglitazone was significantly associated with the incidence of bladder cancer (adjusted HR = 1.22, 95% CI [1.05-1.43] p = 0.01). A dose/effect relationship was observed, with a significant risk for patients receiving a cumulative dose equal to or greater than 28,000 mg (adjusted HR = 1.75, 95% CI [1.22-2.50]) and for durations of exposure of 12 to 23 months (adjusted HR = 1.34, 95% CI [1.02-1.75] p = 0.03) and longer than 24 months [adjusted HR = 1.36, 95% CI [1.04-1.79] p = 0.02). With all the other cancers studied (lung, ENT, colorectal, breast cancer in women and kidney), there was no increase in risk associated with exposure to pioglitazone.

Conclusion:
Analysis of this cohort of diabetic patients followed up in France between 2006 and 2009 does support the hypothesis of a statistically significant connection between exposure to pioglitazone and the incidence of bladder cancer. The observed results are similar to those obtained in the KPNC cohort.

4.2.3. Assessment of the benefit/risk ratio by the MA Committee

The MA Committee meeting of 7 April 2011 re-examined the risk/benefit ratio for pioglitazone and the pharmacovigilance data reported at that meeting emphasised the increased risk of bladder cancer in diabetic patients treated with pioglitazone (ACTOS, COMPETACT). Following a rise in the number of spontaneous notifications of bladder cancer, Afssaps and CNAMTS (French National Salaried Workers' Health Insurance Fund) launched a large retrospective cohort study involving more than 200,000 patients treated with pioglitazone in France between 2006 and 2009, the final results of which are presented above.
The EMA instituted a reassessment of the benefit/risk ratio of pioglitazone-based proprietary medicinal products. This reassessment is still in progress.

On 9 June 2011, Afssaps decided to suspend the use of pioglitazone-containing medicines as from 11 July 2011.

[28] Risk of bladder cancer in diabetics treated with pioglitazone in France: cohort study on the SNIIRAM and PMSI data. *National Health Insurance Fund, Paris, France. Final report from 7/06/2011*
[29] SNIIRAM contains exhaustive individualised and anonymised data on all healthcare expenditure reimbursements. This information can be linked with the PMSI database which provides medical information for all hospitalised patients, including the ICD-10 (version 10 of the International Classification of Diseases) diagnostic codes. The information relating to pioglitazone exposure was collated from the SNIIRAM reimbursement data. The onset of bladder cancer was determined from the PMSI hospitalisation data.

5 DRUG USAGE DATA

5.1. Prescribing information

According to IMS data (cumulative rolling prescription volume to February 2011), ACTOS proprietary medicinal products were the subject of 546,000 prescriptions in the MA indication at the average daily dosage of 1.1 tablets regardless of the presentation (15 mg or 30 mg).

5.2. Data on practical use

The post-registration DUETTO Study was being called for by CEPS as early as 2002 and by the transparency Committee in 2004, the aim being to describe the methods of using pioglitazone, its impact on HbA1c, as well as its tolerability and its compliance profile.
In 2004, a new CEPS agreement once again reiterated the need to have data available on actual conditions of use, together with the other companies marketing glitazones, and stated that a postmarketing assessment – following the bringing onto the market of the ACTOS/AVANDIA/AVANDAMET range – needed to be put in place. This programme, lasting a minimum of two years, needed to consist of a prospective observational study of real usage conditions in terms of the profile of treated patients, adherence to the SPC, compliance, tolerability and glycaemic control – responder or non-responder, using the ANAES definition – as well as measurement of rates of switch to insulin.
The DUETTO study was launched in 2006. It is a prospective two-year descriptive study involving 1002 type 2 diabetics, starting a treatment with pioglitazone and having been included by 180 general practitioners and 102 specialist consultants (endocrinologists/diabetologists).
In February 2008, a letter from the Takeda company indicated that 34 patients presented serious contraindications and that the doctors concerned needed to be warned (the patients nevertheless remaining included in the observational follow-up phase).
The results presented in the transparency dossier are fairly succinct.
Of the 1002 patients in the study, 891 patients (88.9%) had a follow-up visit and 738 (74%) were followed up for 24 months (in the protocol it had been proposed to have 1300 patients in order to have 1000 assessable patients at the end of the two-year follow-up). Of the cohort as a whole, 597 patients were included by general practitioners and 405 by specialist consultants.
The average age of the patients was 61.3 years and 54.3% of them were men. The average time since diagnosis was 7.3 years (median of 6 years) and 216 patients (21.7%) had had diabetes for longer than 10 years. The age group distribution was as follows: 28.7% of the patients were under 55 years, 36% were between 56 and 65 years and 35.2% were over 66 years. In addition, 47.2% were obese (BMI > 30) and 38.2% were overweight (BMI between 25 and 30).
Of the 837 subjects on whom information was available (83.5%), 15.2% had renal failure (creatinine clearance < 60 ml/minute, with three of the patients having a clearance of between 15 and 30 ml/minute). On the urine test strips (16.6%), proteinuria was found in 28.2% of the cases, albuminuria in 25.2% and haematuria in 3.6%.
Cardiovascular involvement was reported in 28.9% of enrolled patients: hypertension (13.9%), coronary artery disease (8.3%), heart failure (4.2%), smoker's leg (2.4%) and carotid stenosis (1.0%). As regards the blood pressure, 55.5% of the patients were presenting values above the usually recommended target value for hypertensive diabetic patients (systolic pressure > 130 and/or diastolic pressure > 80).
The average HbA1c level was available on inclusion in the case of 954 (95.2%) of the patients, with a mean of 8.1 (± 1.4)% and a median of 7.9%. Moreover, in 44.8% of the patients the HbA1c level was higher at 8%, in 45.9% the level was between 6.5% and 8%, and fewer than 10% of the patients had a level ≤ 6.5%). Seven hundred and seventy-nine (779) patients (81.7%) had an HbA1c level ≥ 7% on inclusion, in line with the 2006 recommendations.

Following the inclusion consultation, 51.3% of the patients were on oral dual therapy, 23.3% on triple therapy, 22.5% on monotherapy and 3% on quadruple therapy including insulin.
The most frequently reported reasons for prescribing pioglitazone were as follows: failure of the oral monotherapy in 52.5% of the patients, the patient's weight (23.9%) and intolerance (25.9%) or contraindication (2.5%) to metformin.
Overall, the indications appearing in the SPC were complied with in the case of 631 of the patients (63.0%). Serious misuse (failure to adhere to contraindications such as cardiac failure and liver cytolysis) was identified in 6.8% of patients: 3.2% of patients had a transaminase level > 2.5 times normal and 3.6% had heart failure.
After treatment, the proportion of patients with an HbA1c < 8% and/or a fall in the HbA1c of at least 0.7 of a point was around 85% and 90%, regardless of the follow-up visit and the speciality of the investigator. The proportion of patients with an HbA1c level < 7% on the other hand stood at around 50%.
A change (rosiglitazone suspended and insulin prescribed during the course of one and the same follow-up visit) was noted in the case of 5.4% of the patients. The proportion of patients remaining on pioglitazone decreased regularly over the course of time: 83.1% were still under treatment at 1 year and 72.1% at 2 years.
Of the 917 patients taken into account in the tolerability population, 71 patients (7.7%) exhibited adverse effects, with the treatment being changed or stopped in 32 patients (3.5%).
The most frequent adverse effects were: peripheral oedema, weight gain, diarrhoea-like gastrointestinal disorders. A cardiac condition was reported in seven patients (0.8%).
Ten deaths occurred during the course of the study and in the case of two of them a connection with the ACTOS treatment was mentioned by the investigator.
Patient compliance with pioglitazone was considered to be total in 86% to 93% of cases according to the investigators and 82% to 87% according to the patients.
In all, the results of this study are fairly succinct and it is not possible to judge from it, in particular, how representative it is. However, these results are similar to those reported within the framework of the post-registration study on rosiglitazone. In general, the conditions for use of pioglitazone were adhered to, and the tolerance profile was in line with that expected for this proprietary medicinal product.

6 TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Reassessment of the actual benefit of the ACTOS proprietary medicinal products in all their indications

Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular complications.
The ACTOS proprietary medicinal products are intended to treat hyperglycaemia.

Efficacy/adverse effects ratio:
The tolerance profile of pioglitazone is of some concern in light of the data given in section 4.2 of this Opinion.
In other words, the efficacy/adverse effects ratio of ACTOS proprietary medicinal products does not seem to be sufficiently favourable.

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

The choice of drug treatment and the treatment objectives need to be adjusted to the particular patient (age, duration of the diabetes, special situations, hypoglycaemic risk, etc.).
Type 2 diabetics are first of all treated with the aid of dietary and lifestyle measures, which need to be pursued at every stage.
Antidiabetics are prescribed when diet and lifestyle changes are no longer sufficient to control blood glucose levels.
The adoption of an active lifestyle and nutritional planning are essential interventions at all stages of diabetes management.

If despite monotherapy at the maximum dose the HbA1c is > 6.5%, there is the option to resort to one of the following dual therapies:

- metformin + insulin secretagogue
- metformin + glitazone
- metformin + alpha-glucosidase inhibitor
- insulin secretagogue + glitazone, for patients who are clearly and persistently intolerant to metformin or where metformin is contraindicated
- or insulin secretagogue + alpha-glucosidase inhibitor (in the case of high post-prandial hyperglycaemia, but this combination is less effective in reducing HbA1c levels than the other combinations).

If the HbA1c level is > 7%, there is the option of using a triple therapy or insulin combined with metformin or other oral antidiabetics apart from pioglitazone.
This treatment strategy is currently under review. The place of GLP-1 analogues and DPP-4 inhibitors still remains to be defined.

The latest guidelines for the EASD (European Association for the Study of Diabetes) and of the ADA (American Diabetes Association)[18] consider that pioglitazone is less well validated than, for example, the metformin + sulfonylurea combination.
Glitazones are recommended only in special cases:[30] when the risk of hypoglycaemia is major and to be avoided.
According to NICE[31] (The National Institute for Health and Clinical Excellence), the recommended dual therapy is metformin + sulfonylurea. If sulfonylureas are contraindicated or poorly tolerated, and the risk of hypoglycaemia is high, then the sulfonylurea can be

[30] Olivia J. Phung et al. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA 2010; 303: 1410-1418.
[31] NICE and diabetes: a summary of relevant guidelines. November 2009

replaced by pioglitazone (or a gliptin). However, since this guideline was published, new and disturbing data about the tolerance of pioglitazone have come to light.
Accordingly, the place of ACTOS proprietary medicinal products in the treatment strategy is hard to define in light of all that is known, but there are treatment alternatives.

Public health benefit
The public health burden which type 2 diabetes represents is substantial. That corresponding to the patient sub-population matching the indications for ACTOS is moderate.
An improvement in the treatment of type 2 diabetics is a public health need and an established priority (French 2003 Law on Public Health).
However, the existing treatments already help to meet this need.
There are no arguments in favour of any benefit from treatment with ACTOS. Moreover, a negative impact on morbidity/mortality from bladder cancer cannot be ruled out.
It is not expected therefore that the ACTOS proprietary medicinal products will have any impact on morbidity/mortality and quality of life.
As a result, ACTOS is not expected to benefit public health.

Conclusion
The actual benefit of ACTOS proprietary medicinal products in their indications as monotherapy, dual therapy and triple therapy and in combination with insulin is **therefore insufficient** to justify their being paid for from public funds in the light of the other therapies available.

6.2. Therapeutic use

Not applicable (see section 6.1.)

6.3. Target population

Not applicable

6.4. Transparency Committee recommendations

The transparency Committee does not recommend continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

The transparency Committee recommends removal from the list of medicines refundable by National Insurance and from the list of medicines approved for use by hospitals and various public services.

The transparency Committee wishes to make clear that, pursuant to Article R.163-21 of the French Social Security Code, it decided on its own account to take on the reassessment of the ACTOS proprietary medicinal products, irrespective of what decisions the European and French Registration Authorities may take in relation to the status of the MAs of these proprietary medicinal products.