HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

2 April 2008

ACTOS 15 mg, tablets
Pack of 28 (CIP: 355 632-4)
ACTOS 30 mg, tablets
Pack of 28 (CIP: 355 635-3)

Applicant: TAKEDA

Pioglitazone

List I
ATC Code: A10BG03

Date of first marketing authorisation: 13/10/2000, varied on 28/08/2003, on 26/10/2006 extension of indication to triple oral therapy (in combination with metformin and a sulphonylurea), on 26/01/2007 extension of indication in combination with insulin;

Reason for request:
- Inclusion on the list of medicines reimbursed by National Insurance as triple oral therapy and in combination with insulin.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Pioglitazone

1.2. Indications

“Pioglitazone is indicated in the treatment of type 2 diabetes mellitus:

as monotherapy
- in patients (particularly overweight patients) inadequately controlled by diet or exercise and in whom metformin is contraindicated or not tolerated.

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

as triple oral therapy in combination with
- metformin and a sulphonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy with the above combinations

Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus patients with insufficient glycaemic control on insulin for whom metformin is contraindicated or poorly tolerated (see section 4.4)”

1.3. Dosage (see SPC)

Pioglitazone tablets are taken orally once daily during or between meals.
Pioglitazone may be initiated at 15 mg or 30 mg once daily. The dose may be increased in increments up to 45 mg once daily.
In combination with insulin, the insulin dose can be continued upon initiation of pioglitazone therapy. If patients report hypoglycaemia, the dose of insulin should be decreased.

Elderly: No dose adjustment is necessary in the elderly subject (see section 5.2).
Renal impairment: No dosage adjustment is necessary in patients with impaired renal function (creatinine clearance > 4 ml/min) (see section 5.2). As no information is available from dialysed patients, pioglitazone should not be used in this population.
Hepatic impairment: Pioglitazone should not be used in patients with hepatic impairment (see section 4.4.)
Children and adolescents; As there are no available data, the use of pioglitazone is not recommended in patients under 18 years of age.

1.1. Contraindications

Pioglitazone is contra-indicated in patients with:
- hypersensitivity to the active substance or to one of the excipients,
- heart failure or a history of heart failure (NYHA),
- hepatic impairment,
- diabetic ketoacidosis.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

A	: DIGESTIVE TRACT AND METABOLISM
A10	: DRUGS USED IN DIABETES
A10B	: ORAL ANTIDIABETICS
A10BG	: THIAZOLIDINEDIONES
A10BG03	: PIOGLITAZONE

2.2. Medicines in the same therapeutic category

Indicated as triple oral therapy in type 2 diabetic patients insufficiently well controlled by metformin and a sulphonylurea;
- AVANDIA (rosiglitazone)
- AVANDAMET (fixed-dose rosiglitazone + metformin combination)

Indicated in combination with insulin in type 2 diabetics patients who show intolerance to metformin or for whom metformin is contraindicated: Not applicable.

2.3. Medicines with a similar therapeutic aim

Indicated as triple oral therapy in type 2 diabetic patients insufficiently well controlled by metformin and a sulphonylurea at maximum tolerated doses:
- insulins
- parenteral incretin mimetics

Indicated in combination with insulin in type 2 diabetics who show intolerance to metformin or for whom metformin is contraindicated:
- sulphonylureas
- intestinal alpha-glucosidase inhibitors

3. ANALYSIS OF AVAILABLE DATA

In support of its application, Takeda submitted the results obtained during:
- A placebo-controlled, morbidity and mortality study (ProActive) in patients treated at baseline by dual oral therapy or in combination with insulin with or without an oral antidiabetic (OAD),
- A study of pioglitazone in combination with metformin and a sulphonylurea or glinide versus placebo, (F PIO 100, about which the registration authorities have not drawn any conclusions; study report available)
- A study of pioglitazone in combination with insulin versus placebo (GLAT)
- Two dose-finding studies (PNFP 014,15 mg or 30 mg of pioglitazone at fixed dose + adjusted dose of insulin and PNFP 343,15 mg or 30 mg of pioglitazone + insulin), not described.

The applicant also submitted:
- Summary data from 15 PSURs (31 January 2007) and PSUR number 16
- Summarised safety data of the studies mentioned above and those of the off-label studies GLAI[1], CHICAGO[2], not described in the rest of this opinion.

In addition, for triple oral therapy, the laboratory presented a comparison between pioglitazone and exenatide using the results from the placebo-controlled studies F PIO 100 and study 115. This appraisal without taking randomisation into account cannot be examined by the Transparency Committee.

1 Goldberg RB, Kendall DM, Deeg MA, et al. GLAI Study Investigators. A comparison of lipid and glycaemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care 2005; 28(7):1547-54
2 Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. JAMA 2006;296:2572-2581

3.1. ProActive morbidity and mortality study *(EC 444)* [3,4,5]

This placebo-controlled study (mean duration 34.5 months) was carried out in type 2 diabetics with pre-existing major macrovascular disease (N=5,238) and not adequately controlled (mean HbA1c = 8.1%) despite diet alone or combined with oral antidiabetics (OAD) with or without insulin. At baseline, 4% of the patients were receiving a diet without hypoglycaemic treatment, 9% were treated by metformin monotherapy, 19% by sulphonylurea monotherapy, 25% by metformin + sulphonylurea bitherapy and 34% of the patients were receiving insulin (on average 46.6 units/day).

The effect of pioglitazone was the same as that of placebo for the time to the first occurrence of one of the events of the composite primary endpoint: death, nonfatal MI (including silent MI), stroke, acute coronary syndrome, cardiac intervention including percutaneous coronary dilatation or coronary artery bypass graft, amputation or arterial revascularisation of a lower limb HR 0.90 95% CI [0.80-1.02], NS.
The previously described safety profile for pioglitazone was confirmed with, however, a higher percentage of hypoglycaemia and oedema. A higher incidence of heart failure was also observed with pioglitazone, with no increase in mortality. Weight gain was observed in certain patients receiving pioglitazone (mean + 3.8 kg).

Efficacy in subgroups:

Analysis of the sub-group of patients treated by dual oral therapy at baseline
A post hoc analysis was conducted on 1,427 patients (27%) who received the metformin + sulphonylurea combination with or without another OAD (711 patients in the pioglitazone group and 716 in the placebo group). The mean dose of metformin was approximately 1700 mg/day. Most patients were treated by glibenclamide 11 mg/day, gliclazide 188 mg/day and182 mg/day or glimepiride 3.7 mg/day. Mean baseline HbA1c was 8.2%.
Reductions in HbA1c were -0.94% (1.29) in the pioglitazone group (N=623) and -0.35% (1.37) in the placebo group (N= 613); difference between treatments - 0.59% ($p<0.0001$).

Sub-group analysis of patients treated in combination with insulin at baseline
Takeda presented numerical data for a post hoc analysis of the reduction in HbA1c observed in the subgroup treated by insulin at baseline in combination or not with other oral antidiabetics, 1760 patients (33.6%, 864 in the pioglitazone group, 896 in the placebo group).
On a descriptive basis*:* the observed reduction in HbA1c was -0.93% (1.409) in the pioglitazone group (N=728) and -0.45% (1.382) in the placebo group (N= 765), with baseline HbA1c levels of approximately 8.5%.

Safety in subgroups:

In the subgroup in combination with dual metformin + sulphonylurea therapy:
a higher percentage of oedema (21.9% versus 14.4%), heart failure (severe 6.2% versus 4.6%) and hypoglycaemia (27.6% versus 20.1%)[6] was observed in the pioglitazone group than in the placebo group.

In the subgroup in combination with insulin:
a higher percentage of oedema (30.7% versus 18.2%), hypoglycaemia (41.4% versus 28.8%) and heart failure (6.3% versus 5.3%) was observed in the pioglitazone group than in the placebo group.

3 Study report.
4 Charbonnel B, et al; PROactive Study Group. The prospective pioglitazone clinical trial in macrovascular events (PROactive): can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5238 patients. Diabetes Care 2004;27:1647-1653
5 Dormandy JA 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.
6 EPAR data for these 3 events

3.2. Triple oral therapy: pioglitazone in combination with metformin and a sulphonylurea

3.2.1. Study F PIO 100[7] versus placebo

Primary Objective: to show that pioglitazone, administered in combination with dual oral therapy including metformin and a sulphonylurea or a glinide[8] at maximum dose, decreases HbA1c levels in comparison with placebo, in type 2 diabetics, not adequately controlled by dual oral therapy with metformin and a sulphonylurea or glinide.
Design: Randomised, double-blind, placebo-controlled comparison.
Inclusion criteria: Type 2 diabetics[9] not adequately controlled (HbA1c ≥ 7% and ≤ 9.5%) by dual oral therapy with metformin (dose ≥ 1700 mg/day) and a sulphonylurea or a glinide taken for at least 3 months.
Exclusion criteria included patients with myocardial infarction during the 6 months prior to study entry and heart failure patients (NYHA I to IV).
Treatments: 299 type 2 diabetics[10] were randomised to receive for 7 months: either pioglitazone 30 mg/day (first 3 months) to 45 mg/day (next 4 months if HbA1c > 6.5%), once daily (N=145), or placebo (N=154).
Primary endpoint: change in HbA1c after 7 months of treatment compared to placebo (expected difference between groups: 0.6%)
Secondary endpoints fasting blood glucose

Results
The primary endpoint was analysed for all patients who received at least one treatment dose, with baseline and post-inclusion HbA1c data (modified ITT).
Treatment discontinuations: 22 patients (8 pioglitazone group and 14 placebo group).
Doses of pioglitazone: 45 mg/day after 3 months for 93% of patients, metformin and sulphonylurea doses were not specified.

Table 1 – Study F PIO 100: combination with metformin and sulphonylurea or glinide

	Pioglitazone 30 mg/day to 45 mg/day	placebo
N (randomised)	145	154
N (modified ITT)	142 (97.9%)	147 (95.5%)
Average age (years)	59.7 ± 9.4 years (range 31 to 79 years)	
Mean baseline BMI (kg/m^2)	29.1 ± 3.2 kg/m^2 (range 21.7 to 36.6)	
• **Change in HbA1c (%)**	N=135	N=141
Mean baseline HbA1c (SD)*	8.18 (0.62)	8.14 (0.69)
Change from baseline, adjusted mean (SD)	**-0.90 (0.07)**	**+0.27 (0.07)**
Difference between groups, adjusted mean (95% CI)	**-1.18** (-1.39,-0.96) **p <0.001**	
• Change in fasting blood glucose (mmol/l)	N=121	N=127
Baseline fasting blood glucose (SD)	10.4(2.2)	9.7 (2.1)
Change from baseline, adjusted mean (SD)	-2.17 (0.18)	+0.39 (0.18)
Difference between groups, adjusted mean (95% CI)	-2.56 (-3.07,-2.05) p <0.001	

* on modified ITT population

Primary efficacy endpoint: a reduction in HbA1c was observed in the group receiving pioglitazone combined with metformin and a sulphonylurea or a glinide (- 0.90%), whereas an increase was observed in the group treated with metformin and a sulphonylurea or a glinide (+0.27%) alone. (between-treatment difference: -1.18%, 95% CI[-1.39,-0.96], p <0.001).

Safety:

Adverse reactions were observed in 46.2% of the patients in the pioglitazone group versus 22.1% of those in the placebo group. The most frequent events (> 2%) in the pioglitazone group were: weight gain (25% versus 1%), hypoglycaemia (16% versus 3%), peripheral oedema (3% versus 2%) asthenia (2% versus 1%) increase in CPK (2% versus 0%).

7 Study report data,
8 Or with a glinide, protocol amendment 2
9 Serum creatinine < 135 micromol/L in men and <110 micromol/L in women
10 Serum creatinine < 135 micromol/L in men and <110 micromol/L in women

Mean weight gain was +3.9 kg (± 3 kg) in the pioglitazone group versus a stable weight in the placebo group (- 0.2 kg ± 2.2). For those patients who reported weight gain as an adverse reaction, this was +5.8 kg ± 2.3 in the pioglitazone group (37 patients) and +2.0 kg ± 2.8 in the placebo group (2 patients).

Conclusion: in this double-blind clinical study (7 months), conducted in type 2 diabetics not adequately controlled (HbA1c 8.2%) by metformin and a sulphonylurea or glinide, the addition of pioglitazone (30 to 45 mg/day) decreased HbA1c levels compared to the continuation of dual oral therapy with placebo: -0.90 (0.07) versus +0.27 (0.07) difference between treatments: -1.18%, 95% CI (-1.39,-0.96), p <0.001.
In the group of the patients treated by pioglitazone, the most common events (> 2%) were: weight gain (25% vs 1%, mean + 5.8 kg ± 2.3), hypoglycaemia, peripheral oedema, asthenia, increase in CPK.

3.3. Pioglitazone in combination with insulin

3.3.1. GLAT[11] placebo-controlled study

Primary objective: to show that pioglitazone in combination with insulin is superior to insulin alone on the glycaemic control of type 2 diabetics not adequately controlled by insulin monotherapy.
Design: Randomised, double-blind, placebo-controlled comparison.
Inclusion criteria: type 2 diabetics, aged from 30 to 70 years, not adequately controlled (mean HbA1c ≥ 7%) by insulin monotherapy.
The exclusion criteria included: congestive heart failure (NYHA stage II to IV), past medical history of angina, heart valve disease, documented cardiomyopathy with left ventricular hypertrophy (ECG).
Treatments: before randomisation, the patients only received insulin treatment[12] at the optimal dose for 3 months. They then had to reduce the insulin dose by 10% in order to reduce the risks of hypoglycaemia after institution of another hypoglycaemic drug. Insulin therapy could then be adjusted by the patient.
289 type 2 diabetics not adequately controlled by insulin monotherapy were randomised[13] to receive either pioglitazone 30 mg once daily and insulin (N=142), or placebo and insulin (N=147) double-blind for 6 months.
Treatment was continued for an additional 6 months after unblinding.
Primary efficacy endpoint: mean change from baseline in HbA1c after 24 weeks of treatment. Hypothesis of superiority of pioglitazone with a difference between groups of 0.6%;
Secondary endpoints: fasting blood glucose, dose of insulin administered

11 Mattoo V, et al. H6E-MC-GLAT study group. Metabolic effects of pioglitazone in combination with insulin in patients with type 2 diabetes mellitus whose disease is not adequately controlled with insulin therapy: results of a six month, randomised, double-blind, prospective, multicenter, parallel-group study. Clin Ther 2005;27:554-567; rapport d'étude
12 Adjustment of the insulin dose : fasting and preprandial blood glucose< 5.5 mmol/L (< 1g/L), 2-hour postprandial blood glucose < 7.5 mmol/L (1.35 g/L); inclusion criterion for optimisation period: treatment by insulin monotherapy at the dose > 0.6 IU/kg/day as monotherapy and at the dose > 0.3 IU/kg/day in combination with OAD.
13 and received at least one dose of treatment

Results:
The results presented below were obtained during the 6-month analysis of patients who had received at least one dose of treatment, with baseline and post-inclusion data (mean baseline HbA1c of 8.8% and mean diabetes history of 13.5 years).

Table 2 - GLAT study: Pioglitazone in combination with insulin

	Pioglitazone 30 mg/day	placebo
N (randomised)	142	147
Mean age (years)*	58.9 ± 7.1 years (range 38 to 70 years)	
Mean baseline BMI (kg/m^2)*	32.1 ± 4.9 kg/m^2 (range 19.5 to 48.6)	
• **Change in HbA1c (%)**	N=138	N=144
Mean baseline HbA1c (SD)	8.85 (0.11)	8.79 (0.10)
Change from baseline, adjusted LS mean (SD)	**-0.69 (0.09)**	**-0.14 (0.08)**
Difference between groups, LS mean 95% CI	**-0.55** (-0.76,-0.34) **p <0.0001**	
• Change in fasting blood glucose (mmol/l)	N=135	N=139
Baseline fasting blood glucose (SD)	11.36 (0.39)	11.27 (0.37)
Change compared to baseline, adjusted LS mean	-1.45 (0.35)	+0.35 (0.33)
Difference between groups, LS mean 95% CI	-1.80 (-2.66,-0.95) p <0.0001	

*LS: Least square * *according to ANCOVA model * randomised population*

Primary efficacy endpoint:
After 24 weeks of treatment, a larger reduction in HbA1c was observed in the insulin + pioglitazone group than in the insulin monotherapy group: -0.69% versus -0.14%, difference between treatments: -0.55%, 95% CI [-0.76,-0.14]; p<0.0001).
Secondary endpoint:
A reduction in the mean dose of insulin administered in the pioglitazone + insulin group compared to a stable dose in the placebo group was noted (- 11 IU versus + 2 IU, i.e. -0.16 IU/day.kg versus +0.02 IU/day.kg).

Safety:
Treatment discontinuations at 1 year: 15 patients in the pioglitazone group (11%) for weight gain (4), dyspnoea (3), pulmonary congestion (2), peripheral oedema (2), severe coronary syndrome (1), nausea (1), gastrointestinal oedema (1), fluid retention (1) and 5 patients in the placebo group (3%) for weight gain (1) abdominal distension (1), fatigue (1), amputation (1), tremor (1).

Adverse reactions reported more often in the pioglitazone group than in the placebo group after 6 months and one year of treatment:
- hypoglycaemia[14] : 28.2 % versus 15 %; 32.4% versus 21.8 %
- peripheral oedema : 14.1 % versus 3.4%; 19 % versus 7.5 %
- weight gain : 7.7 versus 1.4 %; 12 % versus 2 %

Adverse reactions considered to be treatment-related[15], pioglitazone group versus placebo group after 6 months and one year of treatment:
- hypoglycaemia :12.7 % versus 6.8%; 14.8% versus 10.2%
- peripheral oedema : 9.2 % versus 0.7%; 14.8% versus 2%
- weight gain : 6.3 versus 0.7 %; 11.3% versus 1.4%

Weight gain: at 6 months, pioglitazone group + 4.0 ± 4.0 kg versus +0.2 ± 2.9 kg, at 12 months, pioglitazone group + 5.0 ± 4.8 kg, placebo group. +0.7 ± 3.8 kg

[14] Severe hypoglycaemic episodes: clinical signs of hypoglycaemia, with the assistance of another person and blood glucose levels < 2.8mmol/L (< 0.5 g/L) or rapid recovery after administration of oral glucose, glucagon or IV glucose. Non-severe hypoglycaemic episodes with clinical signs but no assistance of another person whatever the blood glucose levels.
[15] By the investigator

Conclusion: In this 6-month double-blind, placebo-controlled study (GLAT) carried out in type 2 diabetics not adequately controlled (mean HbA1c 8.8%) by insulin monotherapy, the addition of pioglitazone (30 mg/day) significantly decreased HbA1c levels compared to continued treatment with placebo and insulin: -0.69% versus -0.14%, difference between treatments: -0.55%, 95% CI [-0.76,-0.14]; p<0.0001). The incidence of the most frequent adverse events, hypoglycaemia and peripheral oedema, was higher in the pioglitazone group, with a greater weight gain leading to treatment discontinuation in these patients.

3.4. Safety

3.4.1. Undesirable effects (cf. § 4.8 SPC)

Adverse reactions reported with a frequency of more than 0.5% compared to placebo and greater than one isolated case in patients receiving pioglitazone within the framework of double-blind studies are listed below according to the MedDRA classification (by organ class and absolute incidence). Frequencies are defined as follows: very common > 1/10, common > 1/100 and < 1/10; uncommon > 1/1000 and < 1/100; rare > 1/10000 and < 1/1000; very rare < 1/10000; unknown (cannot be estimated from available data). Adverse reactions are presented in order of decreasing seriousness within each frequency group.

Pioglitazone as triple oral therapy with metformin and a sulphonylurea
Very common: hypoglycaemia
Common: weight gain, increased blood creatinine phosphokinase, joint pain

Pioglitazone in combination with insulin
Very common: oedema
Common: hypoglycaemia, bronchitis, weight gain, back pain, joint pain, dyspnoea, heart failure.

Post-marketing data:
Unknown frequency: macular oedema

In controlled clinical trials, the incidence of heart failure reported with pioglitazone was similar to that of the placebo, metformin and sulphonylurea groups, but it was increased when pioglitazone was used in combination with insulin. In a cardiovascular morbidity and mortality study performed in patients with pre-existing major macrovascular disease, the incidence of severe heart failure, when pioglitazone was added to a treatment including insulin, was 1.6% higher than that of the placebo group. However this did not lead to an increase in mortality. Rare cases of heart failure have been reported since the marketing of pioglitazone, but more frequently when pioglitazone was used in combination with insulin or in patients with a history of heart failure.

Data obtained from double-blind and placebo- or active comparator-controlled randomised clinical trials including more than 8,100 patients treated by pioglitazone and more than 7,400 patients treated by comparators and followed up for 3.5 years were analyzed. A higher incidence of fractures was observed in women treated by pioglitazone (2.6%) compared to those treated by a comparator (1.7%). No increase in the fracture rate was observed in men treated by pioglitazone (1.3%) versus a comparator (1.5%).
In the ProActive study, a cardiovascular morbidity and mortality study performed over 3.5 years, 44/870 (5.1%) of the women treated by pioglitazone had fractures versus 23/905 (2.5%) of women receiving the comparator. No increase in fracture rate was observed in men treated by pioglitazone (1.7%) versus a comparator (2.1 %).

3.4.2. Changes to the safety information in the SPC

Since the last assessment of ACTOS by the French Transparency Committee, the SPC has been varied by bolstering the "Warnings and Precaution for Use" section (§ 4.4). The main variations concerned:

- Bolstering the information about fluid retention and heart failure: Institution of pioglitazone at low dose and gradual uptitration in patients at risk of developing HF (e.g. history of myocardial infarction, symptomatic coronary heart disease), examination for signs of HF, weight gain and oedema more particularly in patients with a low cardiac reserve or in combination with insulin, increase in HF in patients with major macrovascular disease, with no increase in mortality; limited evidence in patients aged over 75 years;
- Bolstering of the weight gain section: This weight gain is dose-dependent and may be due to fat accumulation and in some cases associated with fluid retention which may be a symptom of cardiac failure in certain cases.
- Addition of a specific sentence about the onset of hypoglycaemia: as a consequence of increased insulin sensitivity, patients receiving pioglitazone in dual or triple oral therapy with a sulphonylurea or in dual therapy with insulin may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulphonylurea or insulin may be necessary.

Moreover, reports of new-onset or worsening of macular oedema with decreased visual acuity, have been reported with thiazolidinediones including pioglitazone. If patients report disturbances in visual acuity, an appropriate ophthalmological referral should be considered (cf. SPC).

A fracture risk was identified in women treated by pioglitazone during studies and pharmacovigilance follow-up and was drawn to the attention of prescribers (l*etter to prescribers April 2007)*. The fracture risk must be taken into consideration during long-term management of women treated by pioglitazone (cf. SPC)

3.4.3. Reassessment by EMEA[16]

The reassessment of glitazones by EMEA (October 2007) confirmed a positive benefit-risk ratio (pioglitazone and rosiglitazone) in the treatment of type 2 diabetes.

3.5. Conclusion

In the two extensions of indication examined, the Committee reviewed:

- The placebo-controlled studies, FPIO 100 in triple oral therapy, GLAT in combination with insulin
- The morbidity and mortality ProActive study of pioglitazone versus placebo, including 5,238 type 2 diabetics with a history of macrovascular disease for a mean duration of 34.5 months, not adequately controlled (mean HbA1c 8.1%) with diet alone or combined with antidiabetics and which included patients treated by dual oral therapy or by insulin at baseline
- Variations to the SCP (on 20/08/2007)

➢ **As triple oral therapy, in combination with metformin and a sulphonylurea**

- In terms of efficacy, in the PROACTIVE study, the effect of pioglitazone on morbidity and mortality outcomes of type 2 diabetics with a history of macrovascular disease was not demonstrated.
  The analysis of a subgroup of patients not adequately controlled (baseline HbA1c 8.2%) by dual oral therapy (27%) showed that the addition of pioglitazone decreased HbA1c levels compared to continuation of bitherapy. Only a small effect on Hba1c levels was observed (difference between treatments 0.59%).

[16] www.emea.europa.eu/pdfs/human/press/pr/48427707en.pdf - 2007-10-18

In the placebo-controlled study F PIO 100 (duration 7 months) conducted in type 2 diabetics not adequately controlled (mean baseline HbA1c of 8.2%) by treatment with metformin and a sulphonylurea or glinide, the addition of pioglitazone decreased Hba1c levels compared to the continuation of bitherapy (difference between treatments of -1.18%).

- In terms of safety, in the ProActive study subgroup of patients treated by dual oral therapy at baseline, a higher percentage of hypoglycaemia[17] and oedema was observed in the pioglitazone group than in the placebo group. The incidence of heart failure was higher in the pioglitazone group with no increase in mortality.
  In study F PIO 100, the most common events reported in the pioglitazone-treated group were weight gain (in 25% of patients, mean 3.9 kg), hypoglycaemia, peripheral oedema, asthenia and CPK increase.

  New risks were identified. A fracture risk was noted during the studies and drug safety monitoring of women treated by pioglitazone and this was drawn to the attention of prescribers (class effect).
  Cases of macular oedema were also reported (class effect).

- No controlled studies versus an active comparator were submitted to assess metformin + sulphonylurea + pioglitazone tritherapy compared to other alternative treatments (in particular insulin + oral antidiabetic or exenatide+ oral antidiabetic and other triple oral therapies)

➢ **In combination with insulin in patients who show intolerance to metformin or for whom metformin is contraindicated**

- In terms of efficacy, in the GLAT placebo-controlled study (6 months double-blind, 6 additional months after unblinding), the addition of pioglitazone (30 mg/day) decreased Hba1c levels compared to continuation of a placebo and insulin treatment in type 2 diabetics not adequately controlled (mean HbA1c levels: 8.8%) by insulin monotherapy. The size of the observed effect was small (difference between treatments: -0.55%, 95% CI [-0.76,-0.14]; p<0.0001).
  In addition a moderate decline in insulin requirements was only observed in the pioglitazone group (- 0.16 IU/kg). This was not clinically useful as it did not reduce the number of daily injections.
  Moreover, the treatment regimen evaluated in the GLAT study, insulin then addition of an OAD, pioglitazone, does not correspond to current recommendations on the management of type 2 diabetics by insulin: control by an OAD then use of insulin.

  In the PROACTIVE placebo-controlled study (N=5,238, mean duration 34.5 months) which included a group of patients treated with insulin at baseline (33%), the effect of pioglitazone on morbidity and mortality in type 2 diabetics with a history of macrovascular disease was not demonstrated.

  None of these two studies was specifically carried out in patients who show intolerance to metformin or for whom metformin is contraindicated. The exclusion criteria of these two studies included heart failure (stage >II according to the NYHA classification).

- In terms of safety, a higher percentage of hypoglycaemia, oedema and heart failure was observed in the pioglitazone group than in the placebo group during the PROACTIVE study. When pioglitazone was added to a treatment including insulin, the incidence of severe heart failure was 1.6% higher than in the placebo group. However this did not lead to an increase in mortality during the study (cf. SPC).

  In the GLAT study, the incidence of hypoglycaemias and peripheral oedema, was higher in the pioglitazone group with more weight gain leading to discontinuation of treatment. In this study, the mean weight gain was 4 kg after 6 months of treatment.

[17] EPAR data

New risks were identified. A fracture risk was noted during the studies and drug safety monitoring of women treated by pioglitazone and this was drawn to the attention of prescribers (class effect).
Cases of macular oedema were also reported (class effect).

- No data were submitted on controlled studies versus an active comparator (in particular pioglitazone + insulin vs sulphonylurea + insulin) in order to assess the value of the insulin + pioglitazone combination compared to other alternatives (insulin titration or addition of other OAD to insulin).

The European risk management plan includes in particular monitoring of hepatic disorders, heart failure, peripheral oedema, weight gain, neoplastic diseases, macular oedema and fracture risk.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

4.1.1. Triple oral therapy

- Type 2 diabetes is a chronic disease with potentially serious complications.
- ACTOS is used for the treatment of hyperglycaemia.
- According to current data, the efficacy/safety ratio of this proprietary medicine in the extension of indication as triple oral tritherapy is moderate.
- There are alternative oral drugs to this product
- ACTOS is a complementary means of management of type 2 diabetes mellitus

Public Health Benefit:
The public health burden of type 2 diabetes mellitus is high. The subpopulation of patients inadequately controlled by a combination of two oral antidiabetics (OAD) represents a moderate public health burden.
Improved therapeutic management of type 2 diabetics is a public health need[18], in particular for this subpopulation of patients on dual oral therapy.
As triple oral therapy including the proprietary drug ACTOS was not shown to improve morbidity, mortality and quality of life, or at least have a prolonged beneficial effect on HbA1c, and taking into account other alternative treatments to tritherapy with ACTOS (other triple oral therapies, insulin treatment), the expected impact of the product ACTOS is not quantifiable.
Moreover it may be impossible to extrapolate the trial results to clinical practice because of the safety profile of ACTOS (heart failure, oedema, macular oedema, bone fracture risk in women, weight gain).
The proprietary medicine ACTOS will probably not therefore answer an identified public health need including for the sub-population of patients inadequately controlled by dual oral therapy who cannot use insulin.

Consequently, ACTOS is not expected to benefit public health in this indication.

The Actual Benefit of ACTOS in its indication as triple oral therapy is substantial.

[18] Within the scope of identified public health priorities (GTNDO priorities: National Technical Group for Definition of Public Health Goals (DGS-2003))

4.1.2. In combination with insulin in patients who show intolerance to metformin or for whom metformin is contraindicated

- Type 2 diabetes is a chronic disease with potentially serious complications.
- ACTOS is used for the treatment of hyperglycaemia.
- The efficacy/safety ratio of this proprietary medicine in the extension of indication in combination with insulin is moderate according to current data.
- There are alternative medicines to this product.
- ACTOS is an additional means of management of type 2 diabetics

Public Health Benefit:
The public health burden represented by type 2 diabetes mellitus is high. The sub-population of patients concerned by this indication (patients unable to receive metformin and inadequately controlled by insulin, who will benefit from an Insulin-Actos combination) represents a low burden because of its small size.
The improvement in therapeutic management of insulin-treated type 2 diabetics constitutes a public health need[19].
Available data and in particular the failure to demonstrate that ACTOS provides a benefit compared to insulin titration (on the incidence of hypoglycaemias for example) or in comparison with a combination of an another oral antidiabetic and insulin, show that the expected impact of ACTOS on the intermediate endpoint HbA1c and *a fortiori* on morbidity, mortality and quality of life is not quantifiable.
Moreover it may be impossible to extrapolate the trial results to clinical practice because of the safety profile of ACTOS (heart failure, oedema, macular oedema, risk of bone fracture in women, weight gain).
The proprietary drug ACTOS should not therefore provide a response to an identified public health need.

Consequently, ACTOS is not expected to benefit public health in this indication.

In its indication in combination with insulin, taking into account the small size of the effect, the poor safety profile of the insulin + pioglitazone combination (weight gain, increase in heart failure in particular), and the existence of effective alternative drugs, the French Transparency Committee consider that the Actual Benefit of ACTOS is moderate.

4.2 Improvement in Actual Benefit:

ACTOS, as triple oral therapy in combination with metformin and a sulphonylurea, does not improve actual benefit (level V), but represents a complementary means of management of type 2 diabetics, inadequately controlled by a metformin + sulphonylurea combination.

ACTOS, in combination with insulin in patients who show intolerance to metformin or for whom metformin is contraindicated, does not improve actual benefit (level V) in the management of type 2 diabetes.

4.3 Therapeutic use

According to the guideline “Medication for type 2 diabetes” published by Afssaps and HAS in November 2006, the initial treatment of type 2 diabetes is based on an assessment and realistic changes in lifestyle habits (diet and exercise). The adoption of an active lifestyle and nutritional planning are essential interventions at all stages of diabetes management.
Oral antidiabetics should be prescribed when diet and lifestyle changes (DLC) are no longer sufficient to control blood glucose levels: HbA1c > 6 %. There are 4 therapeutic classes: metformin, intestinal alphaglucosidase inhibitors (AGI), insulin secretors, glitazone.

[19] within the scope of identified public health priorities (GTNDO priorities: National Technical Group for Definition of Public Health Goals (DGS-2003))

These guidelines do not integrate two antidiabetic drugs that obtained an MA after the publication of the guidelines in the therapeutic strategy for management of type 2 diabetics: exenatide, incretin mimetic (MA November 2006) and sitagliptin, dipeptidyl peptidase-4 inhibitor (MA March 2007).

The following treatment may be proposed in patients who fail dual oral therapy with metformin and a sulphonylurea (HbA1c > 7% after 6 months or more of diet and lifestyle changes and correctly conducted dual oral therapy)
- either a test of triple oral therapy: metformin + insulin secretor + glitazone although this combination must be evaluated during long-term use (professional agreement). The goal is to obtain HbA1c levels below 7%.
- or to immediately opt (except with bitherapy including a glitazone) for the addition of insulin (grade C recommendation).

If, despite the failure of correctly conducted triple oral therapy, HbA1c remains ≥ 8% after more than 6 months, glitazones should be stopped and the patient put on insulin (Expert consensus).

Insulin treatment: the addition of dual oral therapy to pre-bed, intermediate or long-acting insulin is recommended as first-line treatment, respecting the contraindication for combination of glitazones with insulin.

NB: These recommendations were established (November 2006) before the extension of indication of ACTOS (January 2007) and the lifting of the contraindication "in combination with insulin" of glitazones.

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

Therapeutic strategy (LTC 8 - Type 2 Diabetes)[20]

HbA1c levels	Treatment	Target HbA1c
HbA1c between 6 % and 6.5 % despite DLC	Metformin monotherapy (or AGI in the case of intolerance or contraindication)	< 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 oral 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 oral therapy and DLC	Insulin ± metformin ± other OAD except glitazone	Reduce HbA1c < 7 %

DLC: diet and lifestyle changes; OAD: oral antidiabetics; AGI: intestinal alphaglucosidase inhibitors

Place of ACTOS:

In its indication in triple oral therapy, the Committee considers that the use of ACTOS must concern type 2 diabetics, with insufficient glycaemic control despite maximal tolerated dose of dual oral therapy with a metformin and sulphonylurea combination.

In combination with insulin in patients for whom metformin is contraindicated or poorly tolerated, ACTOS has an indication recognised by the MA in type 2 diabetes. The role of this proprietary medicine as an adjunct to insulin cannot be specified because of current management guidelines, its low efficacy and the unsatisfactory safety profile of the combination.

[20] Management of diabetes: Type 2 Diabetes. Physician's Guide - Long-term condition, HAS - May 2006

4.4 Target Population

The target population of ACTOS, as defined in the extensions of indications of the MA, corresponds:
for the indication as triple oral therapy

- to type 2 diabetics and in particular overweight subjects failing correctly conducted dual oral therapy with metformin and a sulphonylurea at maximum tolerated dose (HbA1c >7 %)

for the indication in combination with insulin

- to type 2 diabetics inadequately controlled (HbA1c > 7% or >8%) by insulin and in whom metformin is contra-indicated
- to type 2 diabetics inadequately controlled by insulin (HbA1c > 7% or >8%) and who show intolerance to metformin

Data of the study conducted using the permanent Sample of Members of National Insurance Scheme (EPAS) established by the Health Insurance Fund for Salaried Workers (CNAMTS)[21] indicate that the prevalence rate of diabetes treated in Metropolitan France for all regimes was 3.8% in 2005 with a mean annual increase between 2000 and 2005 of 5.7%. On the basis of these percentages and assuming that the mean annual increase noted between 2000 and 2005 was the same as between 2005 and 2006 and remained constant in 2007, the number of diabetic patients treated in 2007 would be approximately 2,485,000 patients[22].
91% of these patients are type 2 diabetics (ENTRED 2001-2003 – diabetes network N°29 – September 2006).
According to the partially published results of the ECODIA 2 study (Diabetes networks N°31 – March 2007): 83.2% of type 2 diabetics are treated by an OAD without insulin, 24.6% by metformin and a sulphonylurea; 14.1% of type 2 diabetics are treated by insulin (5.5% by insulin alone).
Data from the ECODIA 2 study indicate that 51.5% of patients have a HbA1c higher than 7% and 20.5% a HbA1c higher than 8%;
The percentage of patients with a contraindication to metformin and who may receive a glitazone is not precisely known. We assumed that 10% of patients present such a contraindication (expert opinion).
The percentage of patients showing intolerance to metformin is poorly documented[23]. We assumed that 10% of patients are concerned. (Within this group, the percentage of patients who may receive a glitazone is not known).

Triple oral therapy:

- 83.2% of type 2 diabetics are treated by oral antidiabetics without insulin, including 24.6% who receive dual oral therapy with metformin and a sulphonylurea,
- 51.5 % of patients have a HbA1c above 7 %.

On this basis, the population of patients failing correctly conducted dual oral therapy with metformin and a sulphonylurea is 238,400 persons.

According to the ECODIA 2 results, 40.2% of type 2 diabetics are overweight (BMI between 25 and 30 kg/m^2) and 37.9% are obese (BMI above 30 kg/m^2).
If these patients are considered to be the preferential target of the indication for ACTOS as triple oral therapy, the target population of ACTOS would then be not more than 191,600 patients.

In combination with insulin

- 14.6% of type 2 diabetics are treated by insulin, including 5.5 % by insulin alone
- 51.5% of patients have an HbA1c above 7% and 20.5% of patients have an HbA1c above 8%
- Not more than 20% of type 2 diabetics show intolerance or have a contraindication to metformin and may be given glitazones.

[21] Treated diabetes, WHAT changes between 2000 and 2005, Prat Organ Healthcare 2007; 38 (1):1-12
22 on the basis of the INSEE population on 1 January 2008
23 Krentz, Drugs 2005: 65 (3):385-411

The population of patients failing (HbA1c>7%) correctly conducted treatment by insulin, as monotherapy or in combination with an oral antidiabetic, for whom metformin is contraindicated or poorly tolerated, is between 12,800 by insulin monotherapy and 32,800 persons, by insulin alone or combined with an OAD.

If patients with an HbA1c >8% are considered to be the main target of the indication for ACTOS in combination with insulin, the corresponding target population i.e. that of patients failing correctly conducted treatment by insulin with or without an oral antidiabetic (HbA1c >8%), and who show intolerance or have a contradiction to metformin is between 5,100 and 13,100 persons.

5. Transparency Committee Recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicinal products approved for use by hospitals and various public services in the two new indications and at the dosages of the MA.

Packaging: The Committee underlines that in accordance with its deliberation dated 20 July 2005 it recommends, for treatments lasting for one month, a harmonisation of the package size to 30 days.

Reimbursement rate 65%