European Medicines Agency
Post authorisation Evaluation of Medicines for Human Use

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Product Name: **Actos**
Procedure No. **EMEA/H/C/285/II/25**

SCIENTIFIC DISCUSSION

1. INTRODUCTION

Pioglitazone is a (2,4) thiazolidinedione (TZD) derivative that is an orally active ligand for the peroxisome proliferator activated receptor γ (PPARγ).

Pioglitazone is currently approved in the EU with the following indications:

- *As monotherapy in type 2 diabetes mellitus patients, particularly overweight patients, inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance.*
- *In dual oral combination therapy with metformin or a sulphonylurea, in type 2 diabetes mellitus patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or sulphonylurea. The combination with metformin is particularly for overweight patients and the combination with sulphonylurea only for patients who show intolerance to metformin or for whom metformin is contraindicated.*

The MAH submitted this Type II variation to include the use of pioglitazone in combination with insulin, primarily as a result of clinical trial data from the completion of a large macrovascular outcome study of pioglitazone in patients with type 2 diabetes mellitus, known as 'PROactive' (protocol reference AD-4833/EC444), performed following a commitment made to the CPMP in June 2000. The MAH was of the opinion that the results of this study, showing that pioglitazone given in combination with current antidiabetic therapy, including insulin, reduced the risk of macrovascular events in patients with pre-existing macrovascular disease, justified the widening of the therapeutic indication for use of pioglitazone, including combination therapy with insulin.

2. CLINICAL ASPECTS

The MAH submitted the following evidence in support of its application:

- Three clinical trial reports on the efficacy and safety of pioglitazone in combination with insulin in the treatment of Type 2 diabetes as follows (see Table 1):
    - Two previously submitted clinical trial reports (PNFP-014 submitted as part of the original MAA and PNFP-343, a commitment study submitted in 2002)
    - One newly submitted clinical trial report (GLAT) interim 48 week analysis of study FTC-202;
- An analysis of the completed study EC444 (PROactive), a randomised, double-blind, multicentre, placebo-controlled, parallel-group phase 3b cardiovascular outcomes study, in patients with advanced type 2 diabetes and pre-existing macrovascular disease, which included 1760 patients on insulin therapy at baseline.

Table 1: Overview of pioglitazone and insulin combination studies

Study	Treatment Duration	Treatments	N (ITT)	Critical Design Features	Primary Variable
PNFP-014	16 weeks	Pioglitazone 15 mg + existing insulin therapy	191	Fixed dose of pioglitazone; the investigator could adjust the insulin dose.	HbA1c
		Pioglitazone 30 mg + existing insulin therapy	188		
		Placebo + existing insulin therapy	187		
PNFP-343	24 weeks	Pioglitazone 30 mg + existing insulin therapy	345	Fixed dose of pioglitazone; insulin dose could be decreased but not increased	HbA1c
		Pioglitazone 45 mg + existing insulin therapy	345		
GLAT	1 year	Pioglitazone 30 mg + existing insulin therapy	142	3-month insulin optimisation period; fixed dose of pioglitazone; the investigator could adjust the insulin dose	HbA1c
		Placebo + existing insulin therapy	147		

The MAH stated that all of the studies were conducted in accordance with the prevailing ethical standards including those in Directive 2001/20/EC where appropriate.

2.1 Clinical efficacy

PNFP-014: Comparison of Pioglitazone (15 mg and 30 mg) with Placebo as an Add-on to Insulin

Study Design

This was a multicentre, randomised, double-blind, placebo-controlled study of the safety and efficacy of 2 doses of pioglitazone (15 or 30 mg) in combination with insulin compared with insulin alone in patients with type 2 diabetes mellitus whose glucose levels were poorly controlled with their current insulin therapy. Patients who participated in this study were 30 to 75 years of age inclusive, had an HbA1c value greater than or equal to 8.0%, had received insulin therapy of at least 30 units/day for 4 months or longer, and were on a stable, fixed dose of insulin for at least 30 days before the study (with or without metformin, acarbose, or a sulphonylurea).

The primary efficacy variable was change from Baseline in HbA1c. The secondary efficacy variables were HbA1c responder rate defined as a percentage of patients achieving a clinically relevant target value, FPG, fasting C-peptide, triglycerides, and cholesterol (total, HDL-cholesterol, and LDL-cholesterol. Comparisons between placebo plus insulin and each of the 2 pioglitazone plus insulin treatment groups, with respect to changes in the primary and secondary variables, were performed using the Dunnett test with estimates of means and variances obtained from a 2-way ANCOVA model. A total of 566 patients were randomly assigned to treatment and included in the ITT population. Mean age at Baseline was 57 years, and mean BMI was 33.6 kg/m2. Most patients were Caucasian (73%), and slightly more than half (53%) were female. Baseline systolic blood pressure was slightly higher for the groups who received pioglitazone plus insulin than for the group who received placebo plus insulin, but there were no differences among the treatment groups with respect to any other baseline variable.

Results

All treatment groups had statistically significant mean decreases from Baseline in HbA1c throughout the study, and both groups of patients who received pioglitazone plus insulin had a statistically significantly greater reduction in HbA1c than the group of patients who received placebo plus insulin. At Endpoint (Week 16), those who received 15 mg of pioglitazone plus insulin had a mean reduction in HbA1c that was 0.73% (95% CI, -100, -0.47) beyond that observed in the placebo plus insulin group, and the group who received 30 mg of pioglitazone plus insulin had a reduction that was 1.00% (95% CI, -1.27, -0.74) beyond that observed with placebo plus insulin. The reduction in HbA1c levels was reflected in the number of HbA1c responders, as 31.6% of the patients who received placebo, 69.5% who received 15 mg of pioglitazone, and 75.1% who received 30 mg of pioglitazone exhibited

a 0.6 percentage point decrease in HbA1c, a reduction in HbA1c to a level of 6.1% or lower, or both, without requiring an increase in daily insulin dose of 25% or more.

PNFP-343: Dose Comparison of Pioglitazone (30 mg and 45 mg) as an Add-on to Insulin

Study Design
This was a multicentre, randomised, double-blind study of the safety and efficacy of a combination of 30 or 45 mg of pioglitazone and insulin when given to patients with type 2 diabetes mellitus whose glucose levels were poorly controlled by their current insulin therapy. Patients who participated in this study were at least 18 years of age, had an HbA1c value greater than or equal to 8.0%, and were on a stable, fixed dose (at least 30 units/day) of insulin for at least 30 days before the study.

The primary efficacy variable was HbA1c. The secondary efficacy variables were HbA1c responder rate defined as a percentage of patients meeting a clinically relevant target value, FPG, FPG responder rate, and serum lipids (ie, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, and VLDL cholesterol, and free fatty acids (FFA). A total of 345 patients were randomly assigned to each treatment arm, for a total of 690 patients in the ITT population. The mean age for patients was 56.5 years, and mean BMI was 33.19 kg/m2. Approximately two thirds (63.3%) of the patients were Caucasian, and slightly more than half (54.6%) were male. The mean insulin dose (all forms) at Baseline for ITT patients was 69.2 units/day, and 27.1% of the patients reported use of antidiabetes therapy in addition to insulin. There were no major differences between the treatment groups with regard to any of the baseline variables.

Results
The improvements in glycaemic control observed in this study occurred in concert with overall reductions in insulin use by both treatment groups. Statistically significant difference from Baseline in insulin use were first observed at Week 4 for the 45 mg treatment group and at Week 8 for the 30 mg treatment group. The reductions were maintained throughout the remainder of the study, and there was a 4.5 and 7.3 U/d reduction with 30 mg and 45 mg of pioglitazone, respectively, at Endpoint. The reduction in insulin dose was statistically significantly greater in the 45 mg treatment group at all time points.

GLAT: Long-Term Comparison of Pioglitazone (30 mg) with Placebo as Add-on to Insulin

Study Design
This was a multicentre, randomised, double-blind, placebo-controlled study of the safety and efficacy of a combination of 30 mg of pioglitazone plus insulin compared with placebo plus insulin when given to patients with type 2 diabetes mellitus. Patients who participated in this study were 30 to 70 years of age, had an HbA1c of 7.5% or higher at study entry, and were on insulin therapy (with or without oral antidiabetes medications) for 3 months or longer. The duration of double-blind treatment was up to 1 year.

The primary efficacy variable was change from Baseline in HbA1c after 6 months of treatment. The primary efficacy measure was analysed using an ANCOVA model. The secondary efficacy variables were changes from Baseline at 1 year for HbA1c and after 6 and 1 year for FPG, fasting serum C-peptide, fasting serum lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), FFA levels, urinary albumin/creatinine ratio, plasminogen activator inhibitor-1 (PAI-1), C-reactive protein, insulin dose, and rate of hypoglycaemia.

There were 308 patients who entered the insulin optimisation period, and there were 288 who entered the double-blind treatment period and were included in the ITT dataset. Of these patients, 163 were female and 125 were male. The mean age was 58.9 years, and the mean BMI was 32.1±4.9 kg/m2. Most patients (96.5%) were Caucasian, and the mean duration of diabetes was 13.5 years. The mean HbA1c at Baseline of the treatment period was 8.8% in each treatment group, and mean FPG was 11.7 mmol/L for the pioglitazone group and 11.5 mmol/L for the placebo group, suggesting that the study population was not attaining adequate control of glycaemia with insulin alone during the insulin

optimisation period. There were no statistically significant differences between the treatment groups in any of these baseline characteristics.

Results
Despite the 3-month insulin optimisation period, during which efforts were made to optimize each patient's glycaemic control, there was a statistically significant difference between treatment groups after the 1-year treatment period with respect to mean change from Baseline in HbA1c. After 6 months the mean reduction in HbA1c was 0.69 for the pioglitazone group and 0.14 for the placebo group, and this difference was statistically significant (P<0.0001). After 1 year, the mean reduction in HbA1c was 0.58 for the pioglitazone group and 0.13 for the placebo group, a difference that was also statistically significant (P=0.0001). The reduction in HbA1c that occurred with treatment of pioglitazone plus insulin was 0.45 percentage points beyond that observed with placebo plus insulin. In addition, the reductions in HbA1c and FPG that occurred with pioglitazone plus insulin treatment represented statistically significant decreases from Baseline. The improvements in glycaemic control observed in the pioglitazone plus insulin group occurred in concert with a mean reduction in insulin use of 11.4 U/day. This reduction was a significant change from Baseline and significantly different from what occurred in the placebo plus insulin group, which increased insulin use by 4.1 U/day.

PROactive -PROspective PioglitAzone Clinical Trial In MacroVascular Events

This study was a prospective, randomised, double-blind, multicentre, placebo-controlled, parallel-group phase 3b study in patients with type 2 diabetes and pre-existing macrovascular disease. Male and female patients with a diagnosis of type 2 diabetes mellitus, between 35 and 75 years old were screened for eligibility based on results of a medical history, physical examination, and laboratory assessment of alanine aminotransferase (ALT) and glycosylated hemoglobin (HbA1c). Patients who met eligibility criteria and provided written informed consent were randomized to treatment with either pioglitazone or matching placebo.

The study was conducted in 321 clinical sites across 19 European countries.

Study Participants
A total of 5238 subjects (mean age of 62 years), 66% of whom were male and 33% female, were randomly assigned to treatment; 93% of subjects completed the study. Subjects were required to have 1 or more of 6 qualifying criteria of macrovascular disease (entry criteria: myocardial infarction (MI); Stroke; percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG); Acute coronary syndrome; Objective evidence of Coronary artery disease (CAD) or Peripheral arterial obstructive disease). Nearly half of the population had a history of MI and almost 20% had had a stroke. Almost 48% of subjects fulfilled 2 or more entry criteria.

Patients were randomly assigned to receive either pioglitazone or placebo in addition to any existing therapy (including diet and exercise and antidiabetic agents (including insulin), antihypertensives, lipid-lowering agents, and antithrombotic agents) over a treatment period of 2.5 to 4 years. It was a

forced titration study, with the objective of maintaining patients on the maximum tolerated dose of study medication. All patients in the pioglitazone treatment group began treatment at the 15 mg once-a-day (QD) dose and then, based on tolerability, the dose was increased stepwise to 30 mg QD at Visit 2 (Month 1), and 45 mg QD at Visit 3 (Month 2).

Objectives

The study objectives were: Primary, to demonstrate that pioglitazone (15 to 45 mg qd) reduces total mortality and macrovascular morbidity in high-risk patients with type 2 diabetes mellitus, compared to placebo. And secondary, to further characterize the safety of pioglitazone in this group of type 2 diabetes patients.

- **Outcomes/endpoints for efficacy assessment**

Primary Endpoint

The primary endpoint for the study was the following composite:

- All-cause mortality
- Non-fatal MI (including silent MI)
- Acute coronary syndrome
- Cardiac intervention including CABG or PCI
- Stroke
- Major leg amputation (above ankle)
- Bypass surgery or revascularization of the leg

The primary endpoint was analyzed to test the null hypothesis: Pioglitazone is no different from placebo in reducing total mortality and macrovascular morbidity in high-risk patients with type 2 diabetes mellitus. All events that potentially constituted an event within the primary endpoint composite were adjudicated centrally. Analysis of the primary endpoint only considered endpoints confirmed through the Endpoint Adjudication Process. An analysis based on investigator diagnosis was not planned or conducted.

Secondary Endpoints

The following secondary endpoints, in order of priority, were pre-specified in the Statistical Analysis Plan:

- Time to the first occurrence of any of: death from any cause, non-fatal MI (excluding silent MI), stroke.
- Time to cardiovascular death.
- The individual components of the primary endpoint.

All fatal events were classified as cardiovascular unless there was a clear noncardiovascular cause. This classification was carried out through the Endpoint Adjudication Process. For the analysis of cardiovascular mortality, time to death for a non-cardiovascular death was treated as a censored observation.

Subgroup analysis of secondary endpoints was not envisaged; however, the following comparisons were of interest and pre-specified:

- Treatment differences by prior history of acute myocardial infarction (AMI) (yes/no) for the endpoints:
- Time to the first occurrence of any of: cardiovascular death, non-fatal MI (excluding silent MI), stroke.
- Time to the first occurrence of any of: cardiovascular death, non-fatal MI (excluding silent MI).
- Time to the first occurrence of any of: fatal or non-fatal MI (excluding silent MI).
- Treatment differences by prior stoke (yes/no) for the endpoints.
- Time to the first occurrence of any of: cardiovascular death, non-fatal MI (excluding silent MI), stroke.
- Time to the first occurrence of any of: cardiovascular death, stroke.
- Time to the first occurrence of any stroke.

Additional Analyses of Interest

The following measures of interest were believed, a priori, to be variables where differences between the study treatments may be observed:

- The primary endpoint excluding silent MI
- The composite endpoint of cardiovascular death, non-fatal MI (excluding silent MI), and stroke
- The composite endpoint of cardiovascular death and non-fatal MI (excluding silent MI)
- Time to MI (excluding silent MI)
- Cause of death
- Time to start of permanent insulin use (in patients not receiving insulin at the time of randomization)
- Transient Ischaemic Attack (TIA)
- Treatment with retinal photocoagulation
- Carotid intervention
- Use of antihypertensive medication, lipid-lowering medication, oral antidiabetic medication
- Glycemic control: A1C
- Degree of microalbuminuria (Micral test)
- Lipids: HDL cholesterol, LDL cholesterol, triglycerides, ratio of LDL cholesterol / HDL cholesterol

Additionally, study treatments were compared with respect to:

- Number of hospitalizations (hospitalization for any cause except compassionate stay)
- Total number of days in hospital (hospitalization for any cause except compassionate stay)
- Number of days in high dependency units

Diagnosis and Main Criteria for Inclusion

To qualify for study participation, subjects must have had a diagnosis of type 2 diabetes mellitus; been between 35 to 75 years of age, inclusive; were able to comprehend and willing to sign an informed consent form; had a value of A1C above the upper limit of normal (ULN) as determined by the local laboratory at Screening or at any time in the previous 2 months, and had an established history of macrovascular disease defined as 1 or more of the following: MI at least 6 months before entry into the study; stroke at least 6 months before entry into the study; PCI or CABG at least 6 months before entry into the study; acute coronary syndrome at least 3 months before entry into the study; objective evidence of coronary artery disease including any 1 of the following: a positive exercise test, angiography showing at least 1 lesion of more than 50% stenosis of positive scintigraphy at any time prior to entry into the study; or symptomatic peripheral arterial obstructive disease.

Results

- **Baseline data**

The study population was predominantly Caucasian (99%). Means (SD) for other baseline variables were: duration of diabetes, 9.5 (7.02) years; weight, 88.0 (15.57) kg; BMI, 30.9 (4.76) kg/m2; waist circumference, 105.2 (11.90) cm; SBP, 143.4 (17.77) mm Hg; DBP, 83.0 (9.70) mm Hg; and ankle blood pressure, 133.2 (34.65) mm Hg. Demographics and baseline characteristics did not differ significantly between treatment groups. A history of cardiovascular disease was reported for 95% patients, of these 47% had a history of MI, 57.5% had a history of angina, and 75% had a history of hypertension. A total of 59% of patients were current or past smokers, 24% had a history of claudication, and 19% had suffered a prior stroke. A history of retinopathy was reported by 23% of patients with 28.5% of these patients having received photocoagulation treatment, 14% of patients had a history of nephropathy, and 26% had a history of neuropathy. Abnormalities detected on physical examination were reported for 55% of patients, with the highest percentages of abnormalities involving the skin and nervous system (18% for each). No significant differences in physical findings were detected between treatment groups. There were no differences between treatment groups in Baseline laboratory values for HbA1C and lipid levels. At Baseline, 34% of patients were receiving insulin therapy (average 46.6 units per day) in combination with metformin, sulphonylurea, or other agents, 61% were receiving metformin, and 61.5% were receiving sulphonylurea. The pattern of usage with respect to mono- or multiple therapies was similar between treatment groups. Similar proportions of patients in either treatment group were receiving monotherapy with metformin (10%) or

sulphonylurea (19%) or dual therapy with metformin and sulphonylurea (25%). Approximately 30% of patients in either treatment group were receiving insulin with or without oral antidiabetes medication. At baseline, median HbA1c values were 7.8% in the pioglitazone group and 7.9% in the placebo group.

- **Efficacy Results**

Results of the primary composite endpoint analysis showed a 10% relative risk reduction of the first events within the composite for the pioglitazone-treated patients. The Cox proportional hazards model gave an estimate of 0.90 for the hazard ratio comparing pioglitazone with placebo, which did not reach statistical significance (95% CI: 0.80, 1.02; P=0.0954). However, within the primary composite endpoint, fewer disease endpoints (ie, all-cause mortality, non-fatal MI [excluding silent MI], silent MI, stroke, and ACS) were observed in the pioglitazone group, whereas the number of procedural endpoints (cardiac intervention, major leg amputation, leg revascularization) varied between treatment groups. The only first event that occurred more frequently in the pioglitazone group was leg revascularization. Overall, there were fewer total endpoint events in the pioglitazone group (803) compared with placebo (900).

Results of the analysis of the main secondary composite endpoint, a composite of 3 disease endpoints of the primary endpoint (ie, all-cause mortality, non-fatal MI [excluding silent MI], and stroke) showed a statistically significant 16% relative risk reduction of the events within the composite with pioglitazone treatment. The Cox proportional hazards model gave an estimate of 0.84 (95% CI: 0.72, 0.98; P=0.0277) for the hazard ratio comparing pioglitazone with placebo. The results of the primary and main secondary endpoints were not affected by adjustment of significant Baseline covariates in a multivariate model.

Subgroup analyses were performed on several pre-specified subgroups based on demographics, medical history, entry criteria, Baseline laboratory values, and Baseline medications. The trend of benefit with pioglitazone on the primary and main secondary composite endpoints appeared to be consistent across the subgroups.

Additional endpoints were analyzed for the highest risk patients, those with prior MI or prior stroke. Pioglitazone showed a consistent trend of benefit over placebo among patients with prior MI for the time to the first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or stroke; cardiovascular death or non-fatal MI (excluding silent MI); and fatal or non-fatal MI (excluding silent MI). For patients with prior stroke, again pioglitazone showed consistent benefit over placebo for the time to the first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or stroke; cardiovascular death or stroke; and fatal or non-fatal stroke.

The analyses of the other secondary endpoints including the time to first event of the individual components of the primary composite endpoint and cardiovascular mortality showed no statistically significant differences between treatment groups, which was not unexpected because of the relatively smaller number of events for each component. Nevertheless, there were a fewer number of events of allcause mortality, cardiovascular mortality, non-fatal MI, ACS, cardiac intervention, and stroke in the pioglitazone group compared with placebo. In contrast, the incidence of major leg amputation was equal and the incidence of leg revascularization was numerically higher in the pioglitazone group.

Additional “measures of interest” including the composite endpoints of cardiovascular mortality, non-fatal MI (excluding silent MI), or stroke and fatal or non-fatal MI (excluding silent MI) showed statistically significant relative risk reductions of 18% and 23%, respectively, for pioglitazone-treated patients. The composite endpoints including the primary endpoint excluding silent MI and cardiovascular mortality or non-fatal MI (excluding silent MI) were also evaluated and resulted in relative risk reductions of 10% and 14%, respectively for pioglitazone-treated patients, although these reductions were not statistically significant. Other additional measures of interest including deaths caused by MI, hospitalizations (including ICU/CCU admissions), and events of transient ischemic attack were fewer in the pioglitazone group. Generally, no treatment group differences were seen for overall adjudicated causes of death, treatment with retinal photocoagulation, and degree of microalbuminuria.

The composite endpoints of all-cause mortality, MI (excluding silent MI), stroke, or ACS and of cardiovascular mortality, non-fatal MI (excluding silent MI), stroke, or ACS were evaluated. Results of these post-hoc analyses for pioglitazone-treated patients were consistent with those seen for the main secondary endpoint showing statistically significant risk reductions of 17% and 20%, respectively, for these composite endpoints.

Insulin therapy increased markedly by Final Visit in the placebo group, while only a slight increase was seen in the pioglitazone group. Furthermore, the time to permanent insulin therapy was significantly delayed with pioglitazone treatment, as the number of patients progressing to insulin was 50% lower in the pioglitazone group compared with placebo ($P<0.0001$). There was a slight decrease in metformin use over the course of the study in the pioglitazone group, while metformin use increased slightly in the placebo group. The use of lipid-lowering and antihypertensive medications increased similarly in both treatment groups, while the use of loop diuretics increased more in the pioglitazone group than in the placebo group.

Other measures of pharmacological effect included glycemic control and lipid parameters. While A1C was reduced in both treatment groups, the reduction was statistically significantly greater in the pioglitazone group. Pioglitazone also significantly reduced triglycerides and increased HDL cholesterol levels in comparison with placebo. Levels of LDL cholesterol were significantly increased in the pioglitazone group compared with placebo; however, the ratio of LDL to HDL cholesterol was significantly decreased for pioglitazone compared with placebo throughout the study.

Glycaemic and Lipid Effects

At study entry, the vast majority of patients were receiving drug therapy for various cardiovascular-related diseases. The study protocol specified that medications administered to treat underlying cardiovascular disease were to be optimized. Consequently, the use and doses of such medications changed throughout the study. Overall, there was an increased use of lipid-lowering therapy (11% increase in the pioglitazone and 10% increase in the placebo group) and cardiovascular medication (1% increase in pioglitazone and 2% increase in placebo). Throughout the study, patients were to be treated to target for HbA1c levels. Since concomitant oral anti-diabetes drugs and insulin treatment were increased, HbA1c levels decreased over a 3-year period in the placebo group. However, this treatment was still not as effective as adding pioglitazone to the regimen. At final visit, the mean reduction from baseline in HbA1c was 0.9% with pioglitazone and 0.4% with placebo. While the treatment-group difference of 0.5% in the mean HbA1c reduction was statistically significant, it likely cannot entirely explain the cardiovascular benefit noted for pioglitazone. In addition to improvements in glycaemia, pioglitazone significantly improved lipid parameters compared to placebo, despite the similar use of lipid-lowering therapy in both treatment groups. These improvements included reduced triglycerides and LDL/HDL cholesterol ratio and increased HDL-cholesterol levels. Both treatments increased LDLcholesterol levels, but more so in the pioglitazone group such that the treatment-group difference was statistically significant.

2.2 Clinical safety

The safety evaluation in the current submission is based mainly on two previously submitted clinical trial reports (PNFP-014 and PNFP-343) and one newly submitted clinical trial report (GLAT). Cumulatively, more than 1500 patients were studied in these studies, in which more than 1200 received pioglitazone and insulin. In addition to the studies mentioned above, this submission includes data from 1700 patients at high risk for a macrovascular event enrolled in the cardiovascular outcome study EC444. These patients, who entered the study receiving insulin therapy with or without other oral anti-diabetes drugs, formed a large proportion of the total population of over 5200 patients studied for a minimum of 2.5 years and up to 3.5 years.

Overall Extent of Exposure

Studies of Pioglitazone When Used in Combination with Insulin for glycaemic control

A summary of exposure to pioglitazone plus insulin combination therapy during studies PNFP-014, PNFP-343, and GLAT is provided in Table 2. A total of 1545 patients with type 2 diabetes mellitus received at least 1 dose of study drug during these 3 studies. Of this total, 1211 received pioglitazone plus insulin.

In studies PNFP-014 and GLAT, a high percentage of patients who received either treatment completed the studies (between 81% and 92% of patients who received pioglitazone plus insulin and between 87% and 89% of patients who received placebo plus insulin). A slightly higher withdrawal rate was observed during PNFP-343, as approximately 30% of the patients in both treatment groups were withdrawn. Unlike the dosing guidance in the SPC, this study used a fixed-dose regimen of 30 and 45 mg pioglitazone rather than a titration to maximum effect dosing schedule.

Table 2: Summary of Exposure to Pioglitazone When Used in Combination with Insulin

Study No.	Duration of Exposure	Primary Efficacy Variable	Treatments Administered	No. of Subjects (a)		
				Pio + Insulin	Comp + Insulin	Study Total
PNFP-014	16 weeks	HbA1c	Pioglitazone 15 mg + existing insulin therapy	191	--	
			Pioglitazone 30 mg + existing insulin therapy	188	--	
			Placebo + existing insulin therapy	--	187	566
PNFP-343	24 weeks	HbA1c	Pioglitazone 30 mg + existing insulin therapy	345	--	
			Pioglitazone 45 mg + existing insulin therapy	345	--	690
GLAT	1 year	HbA1c	Pioglitazone 30 mg + 90% of current insulin therapy	142	--	
			Placebo + 90% of current insulin therapy	--	147	289
Combined Total				1221	334	1545

Source: PNFP-014, End-of-Text Table 3.1; PNFP-343, End-of-Text Table 3.1; GLAT, Table 10.1.
(a) Includes all subjects who were assigned to treatment and received at least 1 dose of study medication.

Demographic and Baseline Characteristics for Pioglitazone and Insulin Combination Therapy Studies

The results show high incidences of concomitant disease and concomitant medication use, which is typical for a population of patients with type 2 diabetes mellitus. There was a high proportion of concomitant vascular disorders, other metabolic and nutritional disorders, cardiac disorders, and eye disorders. Gastrointestinal, musculoskeletal, nervous system, and reproductive system disorders were also common. The most frequently reported previous and concomitant medications reflected the concomitant disorders, and were consistent with those reported across other clinical trials with pioglitazone. Major differences across studies with respect to use of previous and concomitant medications were mainly due to study-specific methods of data collection (ie, different classification schemes) or study procedures (eg, the high rate of use of ophthalmological agents in PNFP-014 was likely due to the retinal examination completed at the beginning of the study). However, within each study, medication use was balanced across treatment groups.

PROactive study

The data that are presented here include only the subset of patients who were taking insulin in addition to assigned study medication (pioglitazone or placebo) at the beginning of study EC444. Patients may also have been taking OADs, such as metformin or a sulphonylurea, at the same time. Of the 5238 patients included in the total study population, 1760 (33.6%) were receiving insulin at Baseline, and

the use of insulin was well balanced between the treatment groups. Within this on-insulin cohort, 864 of these patients were in the pioglitazone group and 896 were in the placebo group. Duration of treatment with study drug for the cohort of patients who were taking insulin at Baseline was not summarised separately within the EC444 CTR. Mean length of exposure to study medication for the entire study population was 908.2 days in the pioglitazone group and 909.6 days in the placebo group.

Demographic and Baseline Characteristics
The baseline characteristics of EC444 describe a more severely ill patient population than that involved in the glycaemic efficacy studies. They reflect the multiple comorbidities associated with type 2 diabetes mellitus as well as the study's entry criteria, which required patients to have at least 1 of 6 macrovascular diseases or conditions. Almost half of the patients had a history of 2 or more of the 6 conditions. In addition, there was a high incidence of concomitant hypertension and angina. Mean duration of diabetes for baseline insulin users (13 years) was approximately 3 to 4 years longer than for the total study population.

Baseline medication use was commensurate with the conditions and diseases reported.

More than 80% of patients were taking antiplatelet medications, and ACE inhibitors and beta-blockers were each reported by more than half of the patients. The use of ACE inhibitors and loop diuretics was slightly higher in the on-insulin cohort than in the full study population. At Baseline, ACE inhibitors were used by 69% of the on-insulin cohort and 63% of the full study population, while loop diuretics were used by 18% and 14% of each population, respectively. Within the on-insulin cohort, cardiovascular medication use was similar between treatment groups at Baseline.

Antidiabetes regimens principally consisted of insulin in combination with metformin, a sulphonylurea, or both, and use of baseline insulin was well balanced between treatment groups. Since antidiabetes medications were adjusted throughout the study, there was a gradual shift in treatment regimens: A small proportion of pioglitazone-treated patientscould eventually stop taking insulin, whereas more than 10% of patients in the placebo group had to start taking permanent insulin treatment. Despite this, the analysis based on insulin use at Baseline is still meaningful.

ADVERSE EVENTS

AE Data from Pioglitazone and Insulin Combination Therapy Studies
The combination of pioglitazone and insulin was well tolerated both in short-term studies and in the 1-year study. The AEs that were consistently reported at higher rates with pioglitazone than with placebo treatment were oedema and weight increase. The overall incidence of oedema was approximately 2 to 3 times greater than that reported for placebo.

Hypoglycaemia occurred at high incidences in all 3 studies, including the placebo groups. In the 1-year GLAT study, hypoglycaemia was reported for 21.8% of patients receiving placebo plus insulin, compared with 32.4% of those receiving pioglitazone plus insulin. However, hypoglycaemia was rarely treatment limiting and there no fatal events.

Few deaths occurred in any of these studies, and their causes suggested no effect of pioglitazone. The reporting rates of SAEs were similar between 30 mg and 45 mg pioglitazone, and also were similar in both placebo-controlled studies (PNFP-014 and GLAT) between pioglitazone-treated patients and placebo patients.

Over treatment periods of up to 1 year, overall discontinuation rates due to AEs with the pioglitazone and insulin combination were consistent with the overall incidences of common AEs. In PNFP-343, hypoglycaemia, hyperglycaemia, and lower limb oedema were the most common AEs leading to withdrawal; in GLAT, weight increased was the most common.

AE Data from PROactive study
In the on-insulin cohort, a total of 77 (8.9%) patients in the pioglitazone group and 79 (8.8%) in the placebo group died during the study, and the causes of death did not suggest an effect of pioglitazone.

Of the prespecified events of special interest, the most frequently reported primary causes of death were within the category of cardiac ischaemia, and more patients in the placebo group died from these events (2.5% vs 1.9%). There were no other important differences between the treatment groups with respect to the number of deaths attributed to any other preferred term or category of special interest.

In general, there was a higher incidence of AEs in the on-insulin cohort, but this increase was observed for both the pioglitazone and placebo-treated patients. This higher incidence could be due to the more severe underlying disease state for patients within the on-insulin cohort and is not unexpected. With respect to serious heart failure, oedema, and hypoglycaemia the relative increase in reports of these events was not greater for the insulin-treated patients than for those patients who were not treated with insulin. Therefore, the use of pioglitazone in combination with insulin does not appear to amplify the risk for adverse reactions.

SERIOUS ADVERSE EVENTS AND DEATHS

Pioglitazone and Insulin Combination Therapy Studies
Overall, the data do not suggest any increased risk for SAEs within a particular SOC with pioglitazone when added to insulin therapy. In general, as would be expected, the highest incidences of SAEs occurred in the 1-year GLAT study, and in that study the overall incidence of SAEs was similar between the pioglitazone and placebo groups (13.6% vs 13.4%, respectively).

Deaths
In the pioglitazone and insulin combination therapy studies, 6 deaths occurred. The causes of deaths were principally cardiovascular in aetiology, as might be expected in a population of patients with type 2 diabetes mellitus. There was no individual death suggestive of any toxic effect of pioglitazone, and there was no overall increased risk of death with treatment of pioglitazone in the 1-year GLAT study.

PROactive Study
There was a higher incidence of SAEs for the on-insulin cohort overall, but this higher rate was consistent for both the pioglitazone and placebo groups when compared with the non-insulin cohort.

The higher overall rate of SAEs within the on-insulin cohort could be due to the more severe underlying disease state of these patients and is not unexpected. Within the on-insulin cohort, the incidence of SAEs was slightly higher for the placebo group, and this difference was more marked than that observed for the overall study population.

The incidence of myocardial infarction was higher for the on-insulin cohort compared to the non-insulin cohort, but there were fewer events reported for pioglitazone-treated patients in both of these subgroups. Pneumonia was reported more frequently in the pioglitazone group for both the on-insulin and non-insulin cohorts. Overall, most of the serious cases of hyperglycaemia were reported for placebo-treated patients in the noninsulin group, whereas most cases of hypoglycaemia were reported for pioglitazone treated patients in the on-insulin cohort. These 2 findings are not unexpected and likely reflect tighter glucose control for patients in the pioglitazone group. The incidences of cerebrovascular accident were higher in the on-insulin cohort for both treatments, particularly for placebo-treated patients.

The overall incidence of serious heart failure was slightly higher for the on-insulin cohort that for the non-insulin cohort. The increase in reports of serious heart failure with treatment of pioglitazone was not greater than that seen in the non-insulin cohort

Deaths
There was a higher incidence of fatal SAEs for the on-insulin cohort overall, but this higher rate was consistent for both the pioglitazone and placebo groups.

As a result, the incidence of fatal SAEs within the on-insulin cohort was similar for both treatments. The higher overall rate of fatal SAEs within the on-insulin cohort could be due to the more severe underlying disease state for patients and is not unexpected. In general, however, the higher incidence

was consistent for both treatment groups, and the proportion of patients who died because of each fatal SAE was similar for both pioglitazone and placebo-treated patients. The maximum difference between treatment groups in the on-insulin cohort was 0.5 percentage points, which was seen for both sudden cardiac death and sudden death.
Myocardial infarction was the primary cause of death for slightly more placebo patients than pioglitazone patients (1.9% vs 1.5%). No other preferred term was represented by a difference of greater than 0.2% between treatment groups within the on-insulin cohort.

Importantly, the relative difference between treatment groups with respect to the incidences of deaths attributed to each individual category of special interest were very similar to the differences observed for the non-insulin cohort. In the on-insulin cohort, the most frequently reported causes of death were within the special interest category of cardiac ischaemia, and a slightly greater proportion of patients in the placebo group died from these events, as was true for the full study population. There was no difference between the treatment groups with respect to the proportion of patients who died of heart failure.

LABORATORY FINDINGS

Pioglitazone and Insulin Combination Therapy Studies
Small decreases in mean haemoglobin and haematocrit levels were observed in short-term studies with pioglitazone plus insulin. Similar decreases were observed over 1 year of treatment.

There was no increased risk of liver toxicity when pioglitazone was added to insulin as evidenced by consistent decreases in ALT and AST during all 3 pioglitazone and insulin combination therapy studies. Analyses of changes in individual patients showed no excess of pioglitazone patients with changes to >3 times the ULN in liver enzymes compared with placebo over up to 1 year of treatment.

No patients in Study PNFP-014 or PNFP-343 had a markedly abnormal LDH value postbaseline value. In these 2 studies, the incidence of markedly abnormal CPK values ranged from 2.1% to 9.0%, with a corresponding incidence of 2.7% for placebo in PNFP-014.

No negative effects of pioglitazone on variables reflecting renal function were found.

PROactive Study
The EC444 CTR contains a complete description of the results of laboratory evaluations in the overall study population. No subgroup analyses of laboratory results were done for the population of patients taking insulin in addition to pioglitazone or placebo.

In the overall study population, no deleterious effects on liver function were seen with pioglitazone. Incidences of high ALT, AST, or alkaline phosphatase values were low in both groups, and very few patients in either group had elevations to 3 times the ULN in either variable. Compared with placebo, pioglitazone patients showed a trend toward normalisation of high liver function values from Baseline to the Final Visit.

The effects on renal function, as assessed through creatinine measurements, were not distinguishable between pioglitazone and placebo in this study.

DISCONTINUATION DUE TO AES

Pioglitazone and Insulin Combination Therapy Studies

Other Significant AEs
The most common event terms were hypoglycaemia, hyperglycaemia, weight increased, lower limb oedema, and congestive cardiac failure. Incidences were higher in the longer of the two studies (PNFP-343). In the placebo-controlled study, overall incidences were slightly higher for the 2 doses of pioglitazone (2.6% and 3.2%) than for placebo (1.6%).

During GLAT, 15 (10.6%) patients receiving pioglitazone and 5 (3.4%) patients receiving placebo discontinued the study because of an AE. The most common non-serious events leading to discontinuation were increased weight (4 pioglitazone patients and 1 placebo patient), peripheral oedema (2 pioglitazone patients), dyspnoea (2 pioglitazone patients), and pulmonary congestion (2 pioglitazone patients). Of the nonfatal. Three SAEs led to discontinuation—2 in the pioglitazone group (exertional dyspnoea and acute coronary syndrome) and 1 in the placebo group (tremor). Of these 3, only the case of exertional dyspnoea was considered to be related to study drug. Only the event of exertional dyspnoea was considered to be related to study drug.

PROactive Study

Other Significant AEs

Oedema occurred more often in the on-insulin cohort than in the non-insulin cohort and was reported more frequently in the pioglitazone group than in the placebo group. The relative difference between treatment groups was the same for both the on-insulin and non-insulin cohorts.
Hypoglycaemia occurred more often in the on-insulin cohort than in the non-insulin cohort and was reported more frequently in the pioglitazone group than in the placebo group. The relative difference between treatment groups was the same for both the oninsulin and non-insulin cohorts.

2.3 Discussion on clinical aspects of proposed amendments to the product information

The Marketing Authorisation for pioglitazone was granted with a relatively restricted defined use of pioglitazone for the treatment of type 2 diabetes that included a contraindication for its use in combination with insulin. At that time, the CHMP had concerns about thiazolidinedione treatment because of the absence of long-term controlled efficacy and safety data and increased reports of certain adverse events, such as weight gain, oedema, and heart failure.

The present variation application includes three studies evaluating the glycaemic efficacy of pioglitazone in combination with insulin (PNFP–014, PNFP–027 and GLAT) and data from PROactive study, from which 1760 patients (approximately one third of the total study population) were receiving insulin with or without oral anti-diabetes therapies at baseline. Within this on-insulin cohort, the treatment groups were well matched for demographic characteristics. As compared to the total study population, the cohort had a longer duration of disease (13 vs. 10 years), was slightly larger (mean BMIs: 32 vs. 31 kg/m2; mean weight: approximately 90vs 88 kg), and had greater mean HbA1c values (approximately 8.5%vs 8.1%) compared to the overall study population.

Based on the data submitted, the MAH proposed the addition of the following therapeutic indication:

"*Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus patients with insufficient glycaemic control on insulin, alone or in combination with other antidiabetic agents*."

And the deletion of the following contraindication:

"Pioglitazone is also contraindicated for use in combination with insulin".

Discussion on efficacy aspects

Pioglitazone in combination with insulin produced significantly greater improvements in glycaemia compared to insulin alone in the three controlled glycaemia efficacy and safety clinical studies. Consistent with pioglitazone monotherapy and combination therapy studies with either metformin or sulphonylurea, improvements in the HDL-cholesterol and triglycerides levels were observed with pioglitazone in combination with insulin that were not observed with insulin alone. However the value of this effect is not absolutely clear given that the use of statins seems to have been suboptimal in this population. Furthermore, these pioglitazone effects in the presence of insulin were confirmed in the cohort of patients receiving insulin therapy at baseline in PROactive study. Pioglitazone added to

baseline insulin regimens showed significantly better glycaemic control than insulin alone over a treatment period of up to 3.5 years in patients with long-standing type 2 diabetes and significant underlying cardiovascular disease. The beneficial effects of pioglitazone on lipids in EC444 were in addition to those known to be associated with the concomitant lipid-lowering medications used and adjusted throughout the study.

Discussion on safety aspects

The safety profile designed by the data analysed in this variation does not raise new concerns about what was known for pioglitazone, in fact it clears some of the worries about the association with insulin, despite the true risk of heart failure under the association is not completely clear.

Adverse events of oedema and weight gain were reported more frequently with pioglitazone in combination with insulin than with insulin alone.

Within the cohort of patients receiving insulin at baseline in PROactive, a higher reporting rate of heart failure was seen (6.3% with pioglitazone in combination with insulin vs 5.3% with insulin alone) compared to the total study population (5.1% vs 4.1%). Since both insulin and pioglitazone alone are associated with fluid retention and heart failure, the MAH was requested to comment on this issue and to address the benefit/risk balance of pioglitazone in combination with insulin.

On response to this concern from the CHMP, the MAH based its arguments on supportive evidence from:

- The four pivotal studies submitted with the present application, in particular the PROactive study (including a time-to-event meta-analysis of cardiovascular events and deaths reported during double-blind, randomized, comparator-controlled clinical trials of pioglitazone).

- Results from a post-marketing analysis as reported in the Food and Drug Administration-Adverse Event Reporting System (FDA-AERS) database;

- Data from two controlled clinical trials (previously submitted to the CHMP), OPI-504 and OPI-520, which have been completed to determine the safety of pioglitazone in patients with some degree of CHF;

- Preliminary data from a recently completed double-blind, randomised, parallel group study, 01-02-TL-OPI-518, comparing the effects of pioglitazone and glimepiride on the progression of carotid intima-media thickness (CIMT) over 18 months in patients with type 2 diabetes who were asymptomatic for cardiovascular disease; and,

In PROactive a significant reduction of major cardiovascular events of all-cause mortality, stroke, and myocardial infarction was observed for the pioglitazone-treated group. Events of serious heart failure were reported more frequently in the pioglitazone group than in the placebo group; however, mortality was not increased in the pioglitazone-treated patients. A time-to-event analysis of serious heart failure in PROactive showed an increased risk of such an event in the pioglitazone group. However, an analysis of time to first event of serious heart failure or all-cause mortality showed that there was no increased risk for this important outcome.

A systematic analysis based on information contained in the Food and Drug Administration-Adverse Event Reporting System (FDA-AERS) database demonstrated that insulin, as well as combinations of metformin plus insulin plus (first- and second-generation) sulphonylurea derivatives, did not appear to have a synergistic interaction with regard to CHF when added to pioglitazone treatment.

The epidemiological data presented by the MAH, while not conclusive in that some disparities are seen between the 3 studies referred to, suggest that, despite a potentially increased risk of heart failure with TZD treatment, the risk of subsequent mortality was not increased.

In view of all these data, it appears that combination therapy with pioglitazone and insulin is associated with an increased risk of heart failure, but not with an increase in mortality, in particular from the sequelae of heart failure. It should be noted that pioglitazone in the EU is contraindicated in patients with cardiac failure or history of cardiac failure (NYHA stages I to IV). The data reported from the clinical studies and from post-marketing analysis would have included patients with NYHA stages I and II cardiac failure. The most likely scenario, therefore, within the European context, relating to heart failure and such combination therapy would appear to be the precipitation of heart failure in subjects previously not diagnosed as having heart failure. The degree of heart failure, however, would most likely be mild, and could be monitored symptomatically. The precipitation of heart failure, however, must be viewed in the context of the overall improvement in glyaemic control and the absence of any increased mortality.

The CHMP sought advice from the Scientific Advisory Group (SAG) for Diabetes/Endocrinology, that discussed this issue during its meeting of 20 November 2006. The Group agreed that the majority of studies have demonstrated an increase in the overall risk of heart failure, and in the risk of severe heart failure resulting in hospital admission. In the light of evidence from PROactive, the SAG did however acknowledge that this risk could in general be managed effectively with diuretic treatment.

It was noted by the SAG that combinations of TZD and insulin are widely used in other parts of the world, and post-marketing surveillance in the USA showed no evidence of an excess of cardiac failure. It was noted as well that occasional patients did seem to respond particularly well to combination therapy, and that a proportion, perhaps 5-10% of patients, were intolerant of metformin, which is widely used as combination therapy with insulin. It could therefore be argued that such patients should not be denied the possibility of alternative therapy with a glitazone.

On the other hand, it was acknowledged by the CHMP and the SAG that the lack of head-to-head comparisons between metformin plus insulin vs. pioglitazone plus insulin represented a serious gap in the evidence base. On this basis, and given the extra risk of heart failure and added weight gain with pioglitazone, the balance of advantage must still rest with the metformin combination, leaving the combination with pioglitazone as a second option.

The SAG recommendation to the CHMP was that, if the Committee would decide to approve the use of this combination, the following restrictions should be applied: this should be a second-line option with respect to metformin plus insulin, exclusion of patients with all degrees of heart failure, starting treatment with a low dose of pioglitazone and increasing the dose gradually, advice to monitor the patient regularly, and to recommend specialist supervision wherever practicable (whilst acknowledging the difficulty of defining a specialist in the treatment of diabetes). A head-to-head study comparing the combination metformin+insulin versus the combination pioglitazone+insulin is recommended before any wider indication could be considered.

3. PHARMACOVIGILANCE AND RISK MANAGEMENT PLAN

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the effective use of the product.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Hepatic dysfunction	1. Routine pharmacovigilance including review in PSURs. 2. Annual review and report on Hepato-biliary adverse events. 3. Results from completed clinical trials for hepatic events 4. Trend analysis on frequency of reporting.	Contraindication for use in hepatic impairment in section 4.3 of the SPC. Precautions and recommendations for assessing ALT levels in section 4.4 of the SPC. Elevated hepatic function tests and hepatocellular dysfunction in section 4.8.
Heart failure	1. Routine pharmacovigilance continuing annual review in PSURs (analysis by time to onset, exposure, risk factors, concomitant medication including insulin). 2. Analysis from ongoing clinical trials. 3. Final analysis of PROactive long-term trial.	Contraindication in section 4.3 of the SPC. Precautions and recommendations in section 4.4 of the SPC. Heart failure in combination therapy with insulin in section 4.8
Weight gain / peripheral oedema	1. Routine pharmacovigilance including review in PSURs. 2. Results from PROactive study. 3. Analysis from ongoing clinical trials. 4. Pioglitazone clinical trial to investigate mechanisms. 5. Review of ADR reports to assess compliance with SPC recommendations.	Precautions and recommendations in section 4.4 of the SPC.
Neoplasia	1. Routine pharmacovigilance including review in PSURs. 2. Analysis from ongoing clinical trials. 3. Final study report from PROactive study and long term follow up. 4. Analyses from KPNC cohort study. 5. Non-clinical study in male rats.	Statement of finding of bladder hyperplasia / neoplasia in rats in section 5.3 of the SPC.
Macular oedema	1. Routine pharmacovigilance including review in PSURs. 2. Pioglitazone clinical trial to investigate mechanisms.	RMP, risk minimisation for macular oedema: Warning in Section 4.4 of the SPC for macular oedema and decreased visual acuity; mentioning of macular oedema as ADR in Section 4.8 of SPC.

4. CONCLUSION

On the view of the available data and considering the recommendations from the SAG, the CHMP concluded that the data presented is adequate to support the MAH conclusion of an overall positive risk-benefit assessment for the combination therapy of pioglitazone with insulin. Therefore, the CHMP agreed the inclusion of the indication in combination with insulin and the deletion of the contraindication with insulin.

Since the combination therapy of insulin with pioglitazone has not been compared with insulin and metformin, and in view of the risk of cardiac failure, the CHMP was of the opinion that the combination of pioglitazone and insulin should be a second line option to the use of metformin and insulin in patients for whom metformin is inappropriate because of contraindications or intolerance.

In light of the risk of cardiac failure with the use of pioglitazone in combination with insulin, the CHMP requested that this risk should be reflected in detail in the product information and within the Risk Management Plan.

The CHMP requested that the management of the risk should clearly include detailed warnings and precautions for use, including:

- The present contra-indication against use in patients with cardiac failure in Section 4.3 should be retained;
- Clear warnings must be included in Section 4.4 regarding the risk of heart failure and the significance of weight gain;
- Listing of 'heart failure' as an adverse event in Section 4.8;
- A succinct statement in Section 4.8 on reports of heart failure from clinical trials and post-marketing experience.

Additionally, the CHMP agreed that a contraindication to use in diabetic ketoacidosis should be included as pioglitazone exerts its antihyperglyaemic effect only in the presence of endogenous insulin.