

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of Actos. This scientific discussion has been updated until 1 October 2003. For information on changes after this date please refer to module 8B.**

### 1. Introduction

Type 2 diabetes mellitus is a heterogeneous disorder characterised by multiple defects in the pancreatic  $\beta$ -cell, liver, and peripheral tissues such as skeletal muscle and adipose tissue. There is considerable debate about the primacy of insulin resistance or beta cell failure in the disorder. It is well documented that three major metabolic abnormalities contribute to the development of hyperglycaemia in type 2 diabetes mellitus, including impaired insulin secretion in response to glucose, increased hepatic glucose production, and decreased insulin-dependent glucose uptake in the peripheral tissues. The latter two abnormalities are defined as insulin resistance. Insulin resistance is reversed by enhancing the action of insulin, thereby promoting glucose utilisation in peripheral tissues, suppressing gluconeogenesis in the liver, and reducing lipolysis at the adipocyte. Insulin resistance appears in early stages of the disease. It is a major factor in the progression of the disease, contributing to beta cell exhaustion due to demands on insulin secretion.

The prevalence of type 2 diabetes in Europeans is at least 2-3 % and increases substantially in those older than 70 years. Microvascular (retinopathy, nephropathy and neuropathy) and macrovascular complications (e.g., ischemic heart disease) of diabetes are common. Microvascular complications appear to be related to hyperglycaemia. Macrovascular complications are more related to dyslipidaemia and blood pressure control. Diet and exercise are the cornerstones of treatment in order to correct obesity and hyperglycaemia. However, 40 to 60 % of newly treated patients do not respond adequately or fail to comply with diet. Available drug treatments are:

- Sulphonylureas (SU) which increase insulin secretion. Their main adverse effects are hypoglycaemia and weight gain.
- Metformin increases intestinal glucose utilisation, decreases hepatic glucose production and increases insulin sensitivity. Metformin may also improve dyslipidaemia. Gastrointestinal undesirable effects (e.g., diarrhoea in about 15% of patients) and lactic acidosis represent the main adverse effects.
- Alpha-glucosidase inhibitors have shown limited efficacy, but with no risk of hypoglycaemia. Gastrointestinal undesirable effects limit compliance.
- Insulin is used when oral agents have failed to achieve glycaemic control or in case of complications. Insulin may cause hypoglycaemia and weight gain.

The published UK Prospective Diabetes Study (UKPDS) compared intensive care therapy to standard care therapy in a population of 4000 adults over a 9-year period (1977-1997). Results showed a 3-5 % rate of all diabetes-related events per year. Intensive therapy for glycaemia and tight blood pressure control has the potential to reduce the incidence of microvascular complications. In addition, other cardiovascular risk factors including hyperlipidaemia should also be treated. Intensive therapy in the UKPDS produced a non-significant 15 % decrease in macrovascular disease. Decreasing glycated haemoglobin ( $HbA_{1c}$ ) by 0.7 % or achieving fasting plasma glucose  $\leq 6$  mmol/l was found to be crucial and the various agents used had similar efficacy (UKPDS). All treatment groups shared similar outcomes with the exception of the metformin-treated group. Mortality from all causes and from cardiovascular causes was reduced only in the metformin-treated group with intensive plasma glucose control.

Pioglitazone is a thiazolidinedione compound that acts as a peroxisome proliferator activating receptor (PPAR)- $\gamma$  agonist with potential benefits on insulin resistance. Pioglitazone has a different mechanism of action compared to other drugs. It does not stimulate insulin secretion (unlike sulphonylureas), and it does not inhibit glucose absorption (unlike alpha -glucosidase inhibitors). It depends on the presence of insulin for activity.

Pioglitazone is indicated as oral 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.

Pioglitazone is also indicated for oral combination treatment in type 2 diabetes mellitus patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or sulphonylurea:

- in combination with metformin particularly in overweight patients
- in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated

Pioglitazone may be initiated at 15mg or 30mg once daily. The dose may be increased in increments up to 45mg once daily.

## **2. Chemical, pharmaceutical and biological aspects**

### **Composition**

Actos tablets contains pioglitazone hydrochloride as an active substance. Initially, 15 mg and 30 mg strengths were authorized. Subsequently, 45 mg strength was authorised. (see: steps taken after authorisation).

Apart from this difference in strength, the three formulations are identical. The excipients are lactose monohydrate, hydroxypropylcellulose, carmellose calcium, and magnesium stearate which are used as standard excipients, and the choice of the formulation is well justified.

The tablets are fast disintegrating conventional-release dosage forms and the formulation is simple..

The tablets are presented in aluminium blisters sealed with aluminium lidding foil.

### **Active substance**

Pioglitazone hydrochloride is produced by chemical synthesis. Specifications for materials used during synthesis and for the key intermediate are satisfactory. Whilst pioglitazone has one chiral centre, the active substance is produced as the racemate. The individual enantiomers have been tested and found to have similar pharmacological properties. The structure is fully confirmed by spectroscopic methods. The limits proposed for impurities and solvents are acceptable and comply with ICH requirements. Pioglitazone is non-hygroscopic and shows no evidence of polymorphism; it is practically insoluble in water.

Information on the manufacturing process has been updated according to the experience gained since the authorisation. All of these updates have been evaluated and approved as variation procedures (see steps taken after the authorisation).

### **Stability of the Active Substance**

Batches of active substance have been tested for stability under long-term and accelerated conditions. Data show little or no evidence of degradation under any condition tested. The data demonstrate good compliance with the specification, and support the retest period..

### **Other ingredients**

All excipients comply with Ph. Eur. monographs. The applicant states that the lactose used in production of the tablets is obtained from suppliers whose sources are in BSE-free countries and that magnesium stearate is either of plant origin or obtained from suppliers who use stearic acid produced in a BSE-free country.

## **Product development and finished product**

### **Product development**

The formulation is simple, using standard ingredients and the function of the ingredients has been adequately described.

### **Finished product**

The tablets are manufactured in two different sites, both of acceptable GMP status.

The manufacturing process is standard and well described, and the in-process controls are acceptable.

Process validation results from three pilot scale batches of each strength showed consistent results and good reproducibility. Results from three commercial batches of the lowest and highest strengths showed acceptable and comparable results for the two manufacturing sites. The specification for the finished product is typical of a conventional-release tablet, and includes tests with justified limits for content of active substance, uniformity of content, dissolution and microbial contamination. Analytical methods for batch release have been suitably validated.

### **Stability of the Product**

Three batches of each strength were placed in the proposed marketing containers under long-term ICH conditions and 6 months under accelerated conditions.

The stability results of batches stored in the commercial pack support the shelf life and storage conditions stated in the SPC.

### **Bioequivalence**

The formulation of the 15 mg, 30 mg and 45 mg tablets used in all Phase II and Phase III clinical studies were identical to the commercial formulations.

### **Discussion on chemical, pharmaceutical aspects**

The pharmaceutical documentation showed the quality of the product was acceptable. Physicochemical aspects relevant to the clinical performance of the product have been investigated and are controlled in a satisfactory way.

## **3. Toxicopharmacological aspects**

### **Pharmacodynamics**

Experiments were conducted to investigate the effects of pioglitazone on insulin-induced intracellular signalling, glucose and lipid metabolism, glucose tolerance and insulin sensitivity using normal, obese, and genetically hyperglycaemic/obese animals as models of NIDDM and the streptozocin-induced rat model of IDDM. The pharmacodynamic studies support the use of pioglitazone in NIDDM although the mechanism of action is not well characterised at the cellular level.

- *In vitro studies*

It was shown that pioglitazone does not bind to the insulin receptor but is a specific activator of the human PPAR $\gamma$ , and is less potent for the PPAR $\alpha$  and  $\beta$ .

- *In vivo studies*

In mouse, rat and dog models of NIDDM, pioglitazone decreased hyperglycaemia, hyperinsulinemia, and glucose intolerance. Results suggested that insulin was necessary for the action of pioglitazone.

- *General and safety pharmacology programme*

Pioglitazone did not exert relevant effects on the CNS or ANS in mice and cats, or haemodynamics in anaesthetised dogs. Oral pioglitazone produced a significant decrease in urinary volume and sodium excretion in rats compared with placebo or hydrochlorothiazide

### **Pharmacokinetics**

- *Absorption*

Following oral administration, a linear dose: exposure relationship was found but the increase was

slightly sub-proportional in the dose range (0.5-30 mg/kg in rats, 0.1-3.0 mg/kg in dogs). Absorption and bioavailability were high in all species with low first pass effect.

- Distribution

Radioactivity distribution was wide and represented primarily by the parent drug in all tissues. The volume of distribution is low with low distribution to RBC. Pioglitazone is highly bound to plasma proteins, mainly albumin. Rapid chiral inversion was found *in vitro* and *in vivo* in animals and *in vitro* in humans. There was no appreciable accumulation after repeat administration of pioglitazone. Maximum exposure was observed in the liver and brown fat. Radio-labelled pioglitazone and metabolites cross the placenta, and are distributed in foetal tissues and were found in the milk of lactating rats at levels below that found in the maternal plasma. Pioglitazone is not recommended during pregnancy or breast-feeding.

- Metabolism

Metabolism takes place primarily in the liver and kidney. Six major and several minor metabolites have been identified, metabolites MII, MIII and MIV are primarily responsible for the pharmacological activity (MIV is the main metabolite in man). No induction/inhibition of specific hepatic enzymes was found *in vitro*. The major contributors to pioglitazone metabolism were the CYP isoforms 2C8 and 3A4.

- Excretion

In rodents and dogs, most of the administered dose is excreted in the faeces but in monkeys, there is high urinary excretion.

- Toxicokinetics

Toxicokinetic data were obtained in mice, rats, dogs, and monkeys for pioglitazone and for the metabolites MII, MIII and MIV in rats. Data confirm high exposure of the animals to pioglitazone in toxicology studies, although exposure fell with time in most species.

## **Toxicology**

The toxicology programme was performed according to current requirements and all pivotal studies were GLP compliant.

- Acute, single dose toxicity

Single dose toxicity was assessed in mice, rats (oral and ip) and Cynomolgus monkeys (oral gavage). In rats and mice, decreased activity, respiratory depression, and hypo-reactivity were observed. At necropsy, lung hyperaemia, ascites, interlobar adhesion of the liver, and remnant test article in the peritoneal cavity were found. No deaths or clinical signs were observed in monkeys with up to 240 mg/kg oral dose.

- Repeat dose toxicity

Repeated oral dosing studies with pioglitazone were carried out for 13 weeks in mice, and for up to one year in rats, dogs and monkeys. Effects that were evident across species comprised increased body weight and fat mass, decreased haemoglobin, haematocrit, circulating erythrocytes, platelets and protein; prolonged prothrombin time; increased heart and liver weight, proliferation of adipose tissue (increased deposition of white and brown fat and fatty infiltration of bone marrow, spleen and parotid gland), extramedullary haematopoiesis and myocardial hypertrophy. Mortality was dose related, and appears to be related to heart failure or dysfunction. Evidence was provided to demonstrate that these effects, with the exception of cardiac enlargement, were reversible after withdrawal of treatment.

Effects on heart size and myocardial function were examined. A comparative study was carried out in young, lean, normal, and old, fatty, insulin-resistant female beagle dogs for 13 weeks. The study showed a correlation between increased plasma volume and induction of eccentric bi-ventricular cardiac hypertrophy, pericardial and pleural effusion. This study also showed that increases in plasma volume were less marked in fatty (presumed insulin resistant) than lean dogs and that by the end of the study plasma exposure was 20% higher in lean dogs. Further investigations in rodents showed that the susceptibility to increases in heart weight and plasma volume is dependent on 'insulin' status being more easily expressed in normo-glycaemic animals than those with insulin resistance. It was also

shown that co-administration of a diuretic reduces the magnitude of the increases in plasma volume and heart weight associated with treatment of normo-glycaemic rodents with pioglitazone alone.

The no observable effects levels (NOELs) in all of the toxicology species were at plasma exposures that were close ( $\leq 4$  times) to the average human exposure.

- Genotoxicity

The genotoxic potential of pioglitazone was studied in the standard *in vitro* and *in vivo* systems for detection of mutations and chromosomal damage. Additional studies included assessment for induction of unscheduled DNA synthesis in cultured hepatocytes and a bacterial mutagenicity study with concentrated urine obtained from rats given high oral doses of pioglitazone. *In vitro* bacterial and mammalian genotoxicity assays were also carried out with the metabolites (M-I, M-II, M-III, M-IV, M-V, and M-VI). Genotoxic potential was not demonstrated in these studies at non-cytotoxic concentrations.

- Carcinogenicity

Mice and rats were given pioglitazone for 24-months by gavage. In mice there were no other findings than those already noted in repeat dose toxicity studies. There was no evidence of a treatment-related increase in neoplasms. In rats, findings also mirrored the results of chronic toxicity studies. In addition, the urinary bladder showed an increased incidence of epithelial hyperplasia in both sexes. In female rats, the hyperplasia was statistically significantly increased at 63 mg/kg/day. Transitional cell adenoma/carcinoma of the urinary bladder epithelium were seen in males only, at 4 mg/kg/day or more and reached statistical significance at 8 mg/kg/day.. Since pioglitazone is not genotoxic and not carcinogenic in mice, and tumours were only observed in male rats, an epigenetic mechanism of tumourigenesis is probable. It is suggested that urinary calculi formation with subsequent irritation, hyperplasia and metaplasia may be responsible for the carcinogenic response seen in male rats. Analysis of all slides of male urinary bladder from this study suggest that the correlation between the presence of mineralisation and/or urinary calculi, and nodular/papillary hyperplasia and transitional cell tumours in males was 61 %.

A complementary 13-week study was performed in aged rats, which showed that pioglitazone treatment did not increase the incidence of spontaneous calculi formation.

Possible site-specific genotoxicity and a possible role of PPAR activation in the induction/inhibition of apoptosis were discussed. The fact that epithelial hyperplasia and bladder tumours occurred within the clinical exposure range (less than 3 times the human exposure in term of AUC) in male rats was considered..

- Reproduction Toxicity

A standard series of reproduction toxicity studies was conducted with pioglitazone in rats and rabbits.

In fertility studies there was no effect on copulation, impregnation or fertility index. Pioglitazone is non-teratogenic in both rats and rabbits. High doses were associated with maternal toxicity (e.g., placental pathology, weight loss), implantation losses, reduced foetal size, live birth weight and survival ratios, and delayed pup development. It is suggested that the adverse effects on the offspring result from disturbances in maternal physiology rather than a direct toxic effect. This is supported by differences in maternal and foetal NOEL. The foetal NOEL is approximately 3-fold higher than the maternal, which is 2-4-fold the maximum human exposure. Possible effects when physiology is normalised rather than disturbed, cannot accurately be predicted. Available evidence suggests that pioglitazone should not be recommended at any stage of pregnancy. This is reflected in the SPC.

- Environmental Risk Assessment

No environmental impact is anticipated from the clinical use of pioglitazone.HCl.

### **Discussion on toxico-pharmacological aspects**

Pioglitazone and its metabolites are devoid of genotoxic potential as assessed in a standard battery of tests. In carcinogenicity studies, bladder hyperplasia occurred in male rats and high dose group females. Bladder tumours were found in male rats only, at exposure levels close to that of human exposure (less than 3 times the human exposure in term of AUC). This finding was discussed and

particular attention has been paid to human data in this regard. Clinical trial data and the follow up of patients, including urine cytology, did not raise any concern. A case control study will address this issue post marketing. In toxicity studies, in all species pioglitazone was shown to produce heart enlargement and hypertrophy, cardiac insufficiency and plasma volume expansion with oedema, and anaemia, to various extents. Fat tissue increase and/or redistribution were also observed. Most of the effects seen in chronic animal toxicity studies indicated a need for supplementary clinical data and that particular attention be paid to these affected parameters post marketing.

#### **4. Clinical aspects**

##### **Clinical Pharmacology**

The Applicant conducted 28 studies in volunteers or diabetic patients. A total of 445 non diabetic subjects received at least one dose of pioglitazone, including 12 subjects with hepatic impairment, 21 with renal impairment, and 22 elderly subjects. In addition 111 type-2 diabetic patients were studied.

##### **Pharmacodynamics**

- Mechanism of action

Preclinical studies suggested that pioglitazone is a PPAR $\gamma$  agonist that may reduce insulin resistance. PPAR $\gamma$  activation alters patterns of gene expression in target tissues either directly or indirectly. PPAR $\gamma$  activation does not affect insulin production or release.

- Dynamic studies

In healthy volunteers, it was shown that pioglitazone did not produce hypoglycaemia. No consistent changes in insulin and peptide C, or glucose rise after a test-meal, were found but some reduction in post-prandial insulin release was in favour of an improvement in insulin sensitivity.

An open study in type 2 diabetic patients assessed insulin sensitivity by the euglycaemic hyperinsulinaemic clamp technique before and after 12 weeks of pioglitazone (30 mg once daily). Peripheral glucose uptake increased significantly from 5.48 to 8.27 mg/kg/min.

A double-blind, placebo-controlled study was performed using an ‘artificial pancreatic islet’ before and after 12 weeks of treatment. Insulin sensitivity increased with pioglitazone but in the same proportion as with placebo. However, an effect on hepatic glucose uptake was demonstrated.

Other studies in diabetic patients showed improvement in FBG and post prandial BG, the hypoglycaemic effect being sustained for 24 hours. The effect appeared within 2 weeks of treatment. Statistically significant weight gain was observed in patients receiving pioglitazone.

##### **Pharmacokinetics**

Concentrations of pioglitazone and its metabolites in serum and urine were analysed by HPLC and MS detection.

- Absorption

In a single dose, 2-way cross over study, 7 male healthy volunteers received a 7.5-mg oral dose of pioglitazone and an intravenous dose of 5 mg over 2 hrs. Mean absolute bioavailability was more than 80%. Absorption was rapid with maximum serum concentrations,  $C_{\max}$  (typically 900 ng/ml after a 30-mg dose) occurred within 1-3 hr. Exposure (AUC) after oral administration of a 30-mg dose is usually about 8000 ng/ml. Dose proportionality within a dose range of 2-60 mg was shown in single and repeat dose studies.  $T_{1/2}$  was usually between 3-6 hr, and seemed independent of the dose and health status (healthy adults, young or elderly, or diabetics). Two studies on the effect of food on absorption were performed (in Japan and in the US due to differences in diet). Food delayed the rate of absorption from about 2 hr to 3-4 h post dose but the extent of absorption was unchanged.

- Distribution

After iv administration, the volume of distribution was found to be about  $0.25 \pm 0.03$  l/kg. Pioglitazone is highly bound to plasma proteins (97-99 %), mostly albumin.

- Metabolism

Pioglitazone is extensively metabolised in the liver (oxidative biotransformation). Six metabolites have been identified in man (MI-MVI), the main being MIII and MIV (a precursor of MIII and corresponding to the predominant route), both having pharmacological activity, in particular hypoglycaemic activity.

*In vitro* studies on human hepatocytes showed minimal inhibition of pioglitazone on CYP isoforms (1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4). The main contributors were CYP 3A4, 1A1, and 2C8. Pioglitazone had no significant inducing effect on CYP isoforms. Pioglitazone *in vivo* had no effect on the ratio 6- $\beta$ -hydroxycortisol/cortisol in urine indicating no inducing effect on CYP 3A4.

- Elimination

Pioglitazone is slowly cleared from the blood despite the small volume of distribution. Serum concentrations decrease approximately mono-exponentially over time.  $T_{1/2}$  was usually between 3-6 hr and seemed independent of the dose and health status. MIII and MIV metabolites have longer half-lives than the parent compound, of about 27-30 hr. Renal elimination of pioglitazone is negligible. The contribution of renal and biliary routes to the excretion of pioglitazone metabolites was investigated in a mass balance study using  $^{14}\text{C}$ -pioglitazone. Faeces accounted for 55% of the recovered label.

- Special groups

#### Type 2 diabetics

No clinically relevant differences in the main kinetic parameters were observed between healthy volunteers and diabetics. In addition,  $C_{\text{trough}}$  levels of pioglitazone and its metabolites, measured in long-term clinical trials indicated that there was no accumulation.

#### Elderly

Two studies were performed. In elderly Japanese, lower  $C_{\text{max}}$  and AUC values were observed whilst metabolism and clearance seemed unchanged as compared to young healthy volunteers. In the US, elderly had about 20% increase in AUC with a slightly lower oral clearance. However, concentrations and exposure remained in the overall range seen in other studies of non-elderly populations.

#### Renal impairment

The pharmacokinetics of pioglitazone were studied in 27 patients, 6 without renal impairment, 9 with creatinine clearance: 30-60 ml/min and 12 with creatinine clearance < 30 ml/min. As expected renal impairment had no significant effect on pioglitazone kinetics. No metabolite accumulation was observed. No dose adjustment is thus necessary in patients with renal failure.

#### Hepatic impairment

A single dose study was performed in 12 male subjects with mild to moderate chronic liver disease (Child-Pugh score  $\geq 6$ ), and 12 healthy volunteers. After an oral dose of 30 mg pioglitazone, AUCs were comparable. However,  $C_{\text{max}}$  was about 60 % of that of normal subjects. The volume of distribution was increased (155 %) probably due to decreased albumin levels and protein binding. Thus, the unbound fraction of pioglitazone might be increased in patients with liver impairment. Substantially lower levels of MIII metabolite suggested impaired oxidative biotransformation of MIV to MIII. Pioglitazone should not be used in patients with hepatic impairment, this is addressed in the SPC.

#### Obese volunteers

Pharmacokinetic parameters were similar to those of normal healthy volunteers. No dose adjustment seems necessary in obese subjects.

#### Gender effects

Slightly higher values for  $C_{\text{max}}$  and AUC with delayed  $t_{\text{max}}$  were obtained in female subjects due to lower body weight. However, these changes should not be of clinical relevance.

## Children

No clinical studies or trials were performed in adolescents or children. Due to the lack of trials, pioglitazone is not recommended for use in children and adolescents.

- Interaction studies

A formal *in vivo* interaction study was performed with warfarin and showed no changes in pharmacokinetics parameters. Four prospective clinical studies investigated the effect of pioglitazone upon kinetic parameters of concomitantly administered sulphonylureas, metformin, warfarin, phenprocoumon and digoxin. Concomitant administration of pioglitazone had no effect on serum concentrations or protein binding of SUs (glipizide and glibenclamide). SUs had no effect on serum concentrations of pioglitazone. No change in metformin kinetic parameters was found and metformin had no effect on serum concentrations of pioglitazone. There was no indication that pioglitazone (45 mg once daily) altered the efficacy of phenprocoumon or warfarin. The AUC of digoxin was not altered by concomitant administration of pioglitazone.

## Clinical efficacy

The original Marketing Authorisation Application included data from studies in monotherapy and in combination therapy. During the original application, the efficacy of pioglitazone in monotherapy was considered to be insufficiently documented. In subsequent applications (January 2003) additional data were submitted to support the use of pioglitazone in monotherapy and also additional data to support the increase of the maximum daily dose from 30 mg to 45 mg.

The clinical and efficacy programme in the MAA consisted of 19 trials, 3 of which were performed in Europe, 8 in the US and 8 in Japan. Clinical trials are double-blind, randomised, parallel groups, controlled trials. In addition, open trials are presented.

### Double blind studies

Monotherapy included 2017 patients taking pioglitazone (677 patients taking comparator).

Combination therapy included 1518 patients taking pioglitazone (673 patients taking comparator).

The clinical trials were performed according to GCP standards and agreed international ethical principles.

Table 1: Summary of clinical trials with pioglitazone in the MAA (EC: Europe; P: US; C: Japan)

Studies	Study number	Dose (mg od)	N* patients randomised or enrolled/analysed for efficacy	Duration double-blind (weeks)	Primary endpoint
Dose finding	EC 201	15 30	251	26	HbA <sub>1C</sub>
	PNFP-001	7.5 15 30 45	408	26	HbA <sub>1C</sub>
	P-5232-0004	15 30 (in tid)	70	6	FBG
	CPH-010 CCT-001	7.5 15 30 15 30 45	188/161 273/234	8 12	FBG FBG
Monotherapy	EC204	30-45 SU: 2.5-5	270	26	HbA <sub>1C</sub>
	PNFP-012	7.5-15-30/ 15-30-45	260	24	HbA <sub>1C</sub>
	PNFP-026	30	197	16	HbA <sub>1C</sub>
	CCT-011	30	152/134	12	HbA <sub>1C</sub> + FBG



Combination With SU	PNFP-010	SU + Pla SU + 15 SU + 30	560	16	HbA <sub>1C</sub>
	OCT-003	SU + Pla SU + 15 SU + 30 SU + 45	276/237	12	FBG
	CCT-012	SU + Pla SU + 30	149/119	12	HbA <sub>1C</sub> + FBG
Combination with metformin	PNFP-027	Met + Pla Met + 30	328	16	HbA <sub>1C</sub>
Combination with insulin	PNFP-014	Ins + Pla Ins + 15 Insu + 30	566	16	HbA <sub>1C</sub>
Open trials monotherapy	EC202 PNFP-011 OCT-001 OCT-016	15-45 7.5-60 15-45 15-45	238 569 70/61 25/24	52 52 + 48 + 28 +	HbA <sub>1C</sub> HbA <sub>1C</sub>
Open trials combination	OCT-001 SU OCT-015 Vog OCT-016 SU	15-45 15-30 15-45	180/155 52/42 80/63	48+ 12 28+	HbA <sub>1C</sub> FBG + HbA <sub>1C</sub> HbA <sub>1C</sub>

\*Some patients may have participated in more than one trial

#### Patient population

At screening, 60-80 % of patients were considered as not adequately controlled on one or more anti-diabetic agents (HbA<sub>1C</sub> ≥ 8 %). A proportion of naive patients was included in the trials, but was not studied independently of previously treated patients. It should also be noted that type II diabetics with congestive heart failure (CHF) of New-York Heart Association grade III and IV were excluded, but patients with other cardiovascular diseases were not.

#### Endpoints

The primary endpoint was HbA<sub>1C</sub> change from baseline in comparison to placebo in most studies. HbA<sub>1C</sub> is the commonly accepted variable but is not sensitive for short-term evaluations; thus, FBG was the chosen primary endpoint in some short-term studies.

Secondary endpoints included FBG [oral glucose tolerance test (OGTT)], insulin and peptide C. Fasting lipids (triglycerides, HDL-cholesterol and LDL-cholesterol) were measured in most studies.

In some studies, evaluation endpoints included responder rates: responders were defined as patients with a change in HbA<sub>1C</sub> ≥ 0.6 % from baseline to last value, and/or achieving normalisation (i.e., HbA<sub>1C</sub> ≤ 6.1 %). In addition to efficacy endpoints, safety endpoints were recorded (see Safety).

#### Statistical methods

The primary analysis was to test treatment effects between pioglitazone and placebo (analysis of covariance model) with the factor 'treatment' and 'baseline HbA<sub>1C</sub>' as covariates. Last observation carried forward (LOCF) was used for missing values. The Least Significant Difference method was used for pairwise comparisons. P-value and 95 % confidence intervals were calculated.

Results on the ITT population are presented. The ITT population represents all patients with at least one intake of study medication after randomisation and availability of baseline HbA<sub>1C</sub> and at least one post-baseline HbA<sub>1C</sub> value. The Per Protocol population is the ITT population with HbA<sub>1C</sub> value at 12 weeks or later and no major protocol violations before unblinding.

## Dose-response and main clinical trials

### Dose response studies

Table 2: Effect of pioglitazone on HbA<sub>1c</sub> (%; ITT population)

Study	Dose	N /group	Mean baseline	Mean change from baseline
EC 201	Placebo	76	8.75 ± 1.06	-0.34 ± 0.98
	15 mg	83	9.33 ± 1.18	-0.92 ± 1.50
	30 mg	76	9.06 ± 1.20	-1.05 <sup>+</sup> ± 1.25
PNFP-001	Placebo	79	10.41 ± 0.22	+0.74* ± 0.17
	7.5 mg	80	10.04 ± 0.22	+0.20 ± 0.17
	15 mg	79	10.23 ± 0.22	-0.27* <sup>+</sup> ± 0.17
	30 mg	85	10.15 ± 0.21	-0.27* <sup>+</sup> ± 0.17
	45 mg	76	10.34 ± 0.22	-0.86* <sup>+</sup> ± 0.18
P-5232-0004	Placebo	22	8.07	+0.60*
	15 mg	23	7.86	-0.06 <sup>+</sup>
	30 mg	25	7.55	+0.03 <sup>+</sup>
CPH-010	Placebo	40	8.32 ± 1.31	-0.04
	7.5 mg	41	8.61 ± 1.54	-0.15
	15 mg	40	8.60 ± 1.61	-0.23*
	30 mg	40	8.58 ± 1.22	-0.84**
CCT-001	Placebo	60	8.8 ± 1.3	+0.43** ± 0.86
	15 mg	63	9.3 ± 1.7	-0.48* <sup>†</sup> ± 1.51
	30 mg	57	9.5 ± 1.4	-0.95** <sup>†</sup> ± 1.22
	45 mg	54	9.4 ± 1.6	-0.96** <sup>†</sup> ± 1.61

\* p = 0.05 (vs baseline), \*\* p = 0.01 (vs baseline), <sup>+</sup> p = 0.05 (vs placebo), <sup>†</sup> p = 0.01 (vs placebo)

Table 3: Effect of pioglitazone on FBG (mg/dl; ITT population)

		n	Mean Baseline	Mean Change from Baseline	Mean Difference from Placebo
EC201	placebo	76	206.8 ± 46.3	+2.4 ± 46.29	
	15mg	83	234.7 ± 41.7	-34.3 ± 50.76	-21.36 (-35.94, -6.78)
	30mg	76	222.1 ± 65.1	-36.0 ± 62.61	-30.02 (-44.67, -15.38)
PNFP-001	placebo	79	268.1 ± 7.93	+9.4 ± 6.72	
	7.5mg	80	263.2 ± 7.90	-18.1* <sup>+</sup> ± 6.77	-27.5 (-51.0, -4.1)
	15mg	79	267.0 ± 7.94	-29.6* <sup>+</sup> ± 6.78	-39.1 (-62.5, -15.6)
	30mg	84	269.4 ± 7.72	-31.8* <sup>+</sup> ± 6.66	-41.2 (-64.4, -18.0)
	45mg	77	275.5 ± 8.05	-55.9* <sup>+</sup> ± 6.90	-65.3 (-89.0, -41.7)
P-5232-0004	placebo		198.6	+19.1	
	15mg		190.7	-3.6	
	30mg		187.9	-17.0*	
CPH-010	placebo	40	177.1 ± 35.9	+3.2	
	7.5mg	41	192.0 ± 43.0	-12.9**	
	15mg	40	184.2 ± 38.0	-16.8**	
	30mg	40	187.5 ± 35.0	-42.2**	
CCT-001	placebo	60	181.1 ± 23.4	+4.0 ± 26.2	
	15mg	63	191.1 ± 35.7	-22.8** <sup>†</sup> ± 34.7	
	30mg	57	190.0 ± 31.7	-30.1** <sup>†</sup> ± 32.5	
	45mg	54	193.4 ± 32.1	-41.2** <sup>†</sup> ± 37.5	

\*p≤0.05 (vs. baseline), \*\* p≤0.01 (vs. baseline), + p≤0.05 (vs. placebo), <sup>†</sup> p≤0.01 (vs. placebo)

With 30-45mg of pioglitazone there was approximately 0.8 % decrease in HbA<sub>1c</sub> and 30-40 mg/dl decreases in FBG. Effects on secondary endpoints showed similar effects, while unchanged in placebo

groups. Fasting peptide C levels showed a statistically significant decrease in pioglitazone-treated groups. Similar results were observed for fasting insulin levels. Blood glucose in OGTT tests was significantly decreased. A decrease in triglycerides was observed across studies in the pioglitazone treated groups (with the exception of the 15-mg group in CCT-001) when compared to baseline, but not to placebo. No change in total and LDL-cholesterol was found compared to placebo. Statistically significant decreases in free fatty acids were observed at some time points.

No statistically significant changes in diastolic and systolic blood pressure were observed.

Overall, dose ranging studies showed that pioglitazone reduced hyperglycaemia in type 2 diabetics at doses of 15 mg, 30 mg and 45 mg. There was some evidence of a dose-response effect. Doses below 15 mg did not show efficacy, and the doses beyond 45 mg (once daily) did not show additional efficacy.

#### Main clinical trials

- **Monotherapy studies**

There were two monotherapy placebo-controlled trials. With respect to baseline characteristics, US and Japanese patients differed by mean baseline HbA<sub>1c</sub>, FBG and BMI, but in each trial, there were no differences between groups at baseline. Patients were not stratified according to previous treatment (e.g., never treated patients, switched patients and therapeutic failures). Run-in periods were 5 and 4 weeks respectively.

Table 4: Effects on HbA<sub>1c</sub> (%) in Phase III Monotherapy Studies

	PNFP-026 (US)		CCT-011 (Japan)	
	Placebo	30 mg	Placebo	30 mg
n	93	100	63	63
Mean Baseline	10.28 ± 0.19	10.54 ± 0.18	9.19 ± 1.51	9.34 ± 1.70
Mean Change from Baseline	0.76* ± 0.17	0.60* <sup>+</sup> ± 0.17	0.02 ± 0.99	-1.08** <sup>†</sup> ± 1.47
<i>Mean Difference from Placebo</i>	-	-1.37 (-1.83, -0.90)	-	-

\*p≤0.05 (vs baseline), \*\* p≤0.01 (vs baseline), + p≤0.05 (vs placebo) †p≤0.01 (vs placebo)

Table 5: Effects on FBG (mg/dl) in Phase III Monotherapy Studies

	PNFP-026		CCT-011	
	placebo	30mg	Placebo	30mg
N	91	99	63	62
Mean Baseline	270.1 ± 7.87	272.6 ± 7.63	180.7 ± 32.9	185.6 ± 37.3
Mean Change from Baseline	+7.7 ± 6.94	-49.8* <sup>+</sup> ± 6.80	+5.1 ± 29.8	-28.0** <sup>†</sup> ± 33.4
<i>Mean Difference from Placebo</i>	-	-57.5 (-76.7, -38.4)	-	-

\* p≤0.05 (vs baseline), \*\* p≤0.01 (vs baseline), + p≤0.05 (vs placebo), † p≤0.01 (vs placebo)

At endpoint (16 weeks for PNFP-026 and 12 weeks for CCT-011), pioglitazone significantly reduced both HbA<sub>1c</sub> and FBG in both trials as compared to placebo. The effects of pioglitazone on secondary endpoints showed a significant reduction in fasting C-peptide and insulin in PNFP-026.

Triglyceride levels decreased significantly in the pioglitazone-treated group as compared to placebo (p ≤ 0.05) in PNFP-026 and as compared to baseline in CCT011. In PNFP-026, LDL-cholesterol remained unchanged and HDL-cholesterol increased significantly as compared to placebo (p≤0.05).

In controlled monotherapy studies, a mean weight gain of 1.4 kg and 3.0 kg (in European and US trials, respectively) was seen using up to 45 mg pioglitazone.

Considering the chronic nature of type 2 diabetes, these trials are however of short duration (16 and 12 weeks for the US and Japanese trials, respectively). Moreover, the population enrolled was heterogeneous.

Some patients were included after failure of other antidiabetic agents, at least 30% of patients with secondary failure achieved a response defined by a reduction in HbA<sub>1c</sub>  $\geq$  0.6% or a final HbA<sub>1c</sub>  $\leq$  6.1%.

- Monotherapy trial versus active control

This double-blind trial (EC 204) was of 26-week duration, after a 4 to 8-week wash-out period. After 8 weeks of treatment, the study dose (either pioglitazone 30 mg or glibenclamide 2.5 mg) was titrated upward when the change in HbA<sub>1c</sub> did not reach 0.3 % (pioglitazone 45 mg or glibenclamide 5 mg). The glibenclamide dose used in this trial was considered sub-optimal as a 10 or 15-mg maximal dose would have been more appropriate. ANCOVA analysis was carried out to test equal treatment effects between pioglitazone and active comparator.

Table 6: Estimated Treatment Difference for Change from Baseline to Last Value in HbA<sub>1c</sub> (%) – ITT (n=263) and PP Populations (n=196)

	Estimated difference	95 % Confidence Intervals		p-value
		Lower limit	Upper limit	
<b>ITT population</b>				
Pioglitazone versus placebo	-0.72	-1.04	-0.40	0.0001
Glibenclamide versus placebo	-0.96	-1.27	-0.64	0.0001
<i>Pioglitazone versus Glibenclamide</i>	<i>0.27</i>	<i>-0.02</i>	<i>0.55</i>	<i>0.0645</i>
<b>PP population</b>				
Pioglitazone versus placebo	-0.75	-1.12	-0.38	0.0001
Glibenclamide versus placebo	-0.90	-1.27	-0.53	0.0001
<i>Pioglitazone versus Glibenclamide</i>	<i>0.18</i>	<i>-0.13</i>	<i>0.49</i>	<i>0.2464</i>

Pioglitazone as well as glibenclamide showed superior efficacy to placebo. Although the trial was not aimed at comparing glibenclamide with pioglitazone, confidence intervals show that glibenclamide produced greater - although not statistically significant - decreases in HbA<sub>1c</sub> and FBG. This was obtained in spite of sub-optimal doses of glibenclamide. Pioglitazone decreased whereas glibenclamide increased fasting C-peptide levels; there was a statistically significant difference between pioglitazone and glibenclamide.

Pioglitazone decreased diastolic blood pressure compared to both glibenclamide and placebo, but increased systolic blood pressure with a mean change of 1.0 mm Hg.

The mean weight increase was +1.2 kg with pioglitazone as compared to +0.8 kg and -1.5 kg for glibenclamide and placebo, respectively.

LDL-cholesterol values did not differ significantly between groups. HDL-cholesterol values increased in all treatment groups. Pairwise comparison revealed that pioglitazone was associated with significantly greater increases in HDL-cholesterol than placebo (p = 0.01) and glibenclamide (p = 0.0001).

- Forced escalation dose trial

In addition, a placebo-controlled trial was carried out in the US with patients (mean BMI: 30.9 kg/m<sup>2</sup>) receiving increasing doses of pioglitazone (7.5/15/30 mg or 15/30/45 mg, increases after periods of 4 weeks) over 24 weeks. The run-in period lasted for 2-6 weeks. Significant decreases in HbA<sub>1c</sub> and FBG were observed as compared with placebo, but no differences between the 2 active treatment arms.

No changes were observed in fasting peptide-C and insulin, or in blood pressure.

A significant decrease in triglyceride concentrations was found between the 15/30/45 mg and placebo groups at week 16 and 24.

- Long term trials

Four open trials (1162 patients entered, 1095 completed) were performed in order to evaluate tolerability and safety. They included patients from previous controlled trials. In the two Japanese trials (OCT-001 and 016), SUs could be used in combination with pioglitazone; these trials were of 48 and 28 week duration. Both European and US trials (EC-202, PNFP-011 respectively) lasted for 52 weeks.

Overall, comparisons of the decrease in HbA<sub>1C</sub> and FBG showed a slightly greater effect in women than in men, but no differences according to age (<65 y. or ≥65 y.) or previous anti-diabetic drugs used.

In PNFP-011, for HbA<sub>1C</sub> there was a mean decrease from baseline of 1.35% (1.57% for the de novo group of patients and 1.03% for the rollover pioglitazone group); the mean weight change from baseline was 5.56 kg at week 48. At week 48 the percentage of patients classified as responders were 76.2% in the de novo group, 56.5% in the rollover placebo group and 58.8% in the rollover pioglitazone group.

In the Japanese studies, HbA<sub>1C</sub> showed a decrease of 1.17-1.60% in patients taking pioglitazone in conjunction with diet and a decrease of 1.15-1.18% in patients taking pioglitazone in conjunction with SU.

In EC-202, the mean HbA<sub>1C</sub> decrease from baseline was 0.87% and mean weight change from baseline was +1.4 ± 3.8 kg in patients completing one-year treatment with pioglitazone. In the European study, mean total cholesterol increased by 1.9 %, LDL decreased by 0.4 % while there was a rise by 15.2 % in HDL and triglycerides decreased by 7.1 %. Similar results were found in the Japanese study.

No change in blood pressure was observed in these trials.

- Combination therapy

- Combination with sulphonylureas (985 patients)

Three placebo-controlled trials [of which two were double-blind – CCT-012 (12 weeks) and PNFP-010 (16 weeks) and one single-blind OCT-003 (12 weeks)] were performed in patients already receiving sulphonylureas (mostly glibenclamide) at about 60-70 % of the recommended dose. The SU dose was to remain constant throughout the trial (unless hypoglycaemia occurred). Other anti-diabetic agents (e.g., metformin or acarbose) were discontinued. The run-in periods were 1 or 4 weeks for trial PNFP-010, and 4 weeks for OCT-003 and CCT-012.

Table 7: Effects on HbA<sub>1C</sub> (%) in Phase III Combination Studies

	PNFP-010			OCT-003				CCT-012	
	Placebo	15 mg	30 mg	Placebo	15 mg	30 mg	45 mg	Placebo	15 mg
N	181	176	182	59	59	52	58	58	61
Mean BMI (kg/m <sup>2</sup> )	32.0 ± 4.9	31.4 ± 5.0	32.4 ± 7.2	24.4 ± 3.8	24.8 ± 3.5	24.5 ± 3.4	24.7 ± 3.6	24.3 ± 3.4	23.3 ± 3.4
Mean Baseline	9.86 ± 0.105	10.01 ± 0.009	9.91 ± 0.095	9.62 ± 1.46	10.23 ± 1.715	10.32 ± 1.94	9.81 ± 1.55	9.71 ± 1.69	9.884 ± 1.52
Mean Change from Baseline	0.06 ± 0.092	-0.82* ± 0.093	-1.22* ± 0.092	0.47 ± 0.86	-0.65** † ± 1.22	-1.15** † ± 1.17	-1.09** † ± 1.29	-0.08 ± 1.19	-1.24** † ± 1.33
Mean Difference from Placebo		-0.88 [-1.17; -0.58]	-1.28 [-1.57; -1.99]						

\*p≤0.05 (vs baseline), \*\* p≤0.01 (vs baseline), + p≤0.05 (vs placebo) † p≤0.01 (vs placebo)

Significant differences were found for both HbA<sub>1C</sub> and FBG with all 3 doses of pioglitazone + SU as compared to placebo + SU. In PNFP-010, 10.2 % of patients on placebo + SU had HbA<sub>1C</sub> < 8 % at endpoint compared with 28.8 and 36 % in pioglitazone 15 and 30 mg groups + SU.

Between group analysis revealed significant reductions in triglycerides and free fatty acids by pioglitazone + SU as compared with placebo + SU. Between group analysis in both studies PNFP-010 and CCT-012 revealed significant increases in HDL-cholesterol with the 15-mg and 30-mg doses of pioglitazone in combination with SU as compared to the placebo + SU group. LDL-cholesterol values were increased in study PNFP-010 as compared to baseline, but were reduced compared to placebo. LDL was not measured in study OCT-003 or CCT-012.

Body weight increased with all doses of pioglitazone. The heaviest mean weight increase was 3.06 kg in PNFP-010 (pioglitazone 30 mg).

#### Open long term extension studies

A total of 236 patients entered the open extension study (PNFP-031) from the controlled pioglitazone + SU study (PNFP-010). Patients who had been on placebo in the original double-blind study were transferred to pioglitazone (roll-over placebo group) whilst those originally on pioglitazone continued on this therapy (roll-over pioglitazone group). 76 patients had originally been on placebo, and 160 on pioglitazone in the double-blind study. 166 patients completed 48 weeks of treatment, and 137 completed 72 weeks. Metabolic control results show a good maintenance of effect over time, and LOCF values suggest that patients withdrawing did not have a major impact on the results.

The CPMP requested a post-hoc analysis of efficacy (and safety) results in the subset of diabetic population where there might be an unmet medical need, i.e., the patients insufficiently controlled on SU but who cannot tolerate metformin. The Applicant provided information concerning patients possibly not tolerating metformin or in whom metformin is not recommended (i.e., GI symptoms, age  $\geq 65$  years, creatinine  $\geq 1.2$  mg/dl, BMI  $< 25$  kg/m<sup>2</sup>).

In the US controlled trial of the combination SU + pioglitazone (16-week PNFP-010 study), 209 out of 373 patients were not suitable candidates for metformin. Similar changes in HbA<sub>1C</sub> (an approx. 1% reduction) and in FBG to those seen in the total population were found in this group of 209 patients following combination therapy of pioglitazone and SU.

In the Japanese studies, metformin was not indicated or possibly not tolerated in 139/207 patients and in 57/75 patients, OCT-003 and CCT-012 studies respectively. The response to pioglitazone in combination with SU was similar in those patients to that in the total study populations.

Two open long-term studies pioglitazone (15/30/45mg)+ SU combination were conducted in Japan. In OCT-001, 133 patients completed  $\geq 48$  weeks and in OCT-016, 49 patients completed 28 weeks. In OCT-001 and OCT-016, metformin was not indicated or not tolerated in 97 and 42 patients respectively. Changes in HbA<sub>1C</sub> suggest that the 'not indicated / not tolerated' group has similar efficacy to the total groups of patients in OCT-001 and OCT-016.

- Combination with insulin (566 patients)

Patients with type II diabetes, poorly controlled on insulin (chronic treatment  $\geq 4$  months) were randomised either to placebo or pioglitazone for 16 weeks after a 4-week run-in period (PNFP-014). Other anti-diabetic agents were discontinued. The mean BMI was about 33-34 kg/m<sup>2</sup>.

The addition of pioglitazone decreased HbA<sub>1C</sub> (-0.73 % [95%CI:-1.00;-0.47] at 15 mg and -1.00 % [95%CI: -1.27;-0.74] at 30 mg, and fasting C-peptide. Initial insulin dose could be reduced in 2.1 %, 3.7 % and 16 % of the placebo, pioglitazone 15 mg, and 30 mg treated patients, respectively. In PNFP-014, 12.8 % of patients on placebo had HbA<sub>1C</sub>  $< 8$  % at endpoint compared with 31.4 and 41.5 % in pioglitazone 15 and 30 mg groups, respectively.

Body weight gain was observed in patients treated with both pioglitazone doses, the maximum mean increase being +3.9 kg. From week 8, significant reductions in triglyceride levels (insulin+pioglitazone 30 mg) and significant increases in HDL-cholesterol were observed, as compared to insulin+placebo.

Small increases in LDL-cholesterol and total cholesterol were observed in both insulin+pioglitazone groups, but differences were not significant as compared to placebo.

- Combination with metformin (328 patients)

This trial (PNFP-027) compared one dose (30 mg) of pioglitazone + metformin with metformin + placebo in a total of 328 patients (mean BMI: 32 kg/m<sup>2</sup>) poorly controlled (HbA<sub>1c</sub> ≥ 8 %) by metformin (with or without SU or acarbose) over 16 weeks. The run-in period was 1 or 4 weeks. Patients stopped other antidiabetic agents and remained on their current dose of metformin (patient were taking about 60 % of the maximum recommended dose). The dose of metformin was acceptable as the maximum dose is generally poorly tolerated.

HbA<sub>1c</sub> significantly decreased by 0.83 % [95 %CI: -1.15, -0.51] and FBG by 37.7 mg/dl [95 %CI: -49.3, -26.0] in the pioglitazone treated group. Responder rates (i.e., change in HbA<sub>1c</sub> ≥ 0.6 % from baseline to last value, or achieving normalisation: HbA<sub>1c</sub> ≤ 6.1 %) were 54 % and 21.6 % in the pioglitazone and the placebo groups, respectively.

There was no difference in the response obtained in patients treated with either <2000 mg or > 2000 mg metformin doses.

There were statistically significant mean decreases in triglycerides and mean increases in HDL-cholesterol as compared with placebo. LDL-cholesterol was not measured for patients whose triglycerides were >400 mg/dl at a given visit. There were no significant differences in LDL-cholesterol or total cholesterol (TC) between treatment groups although for both measures there were small significant increases from baseline in both treatment groups. The calculated (from the mean values) HDL/TC ratio increased by 10%.

Body weight decreased in the metformin + placebo group (-1.36 kg) and increased in the metformin + pioglitazone group (+0.95 kg). The difference between groups was not significant.

#### *Open long term extension study*

154 patients from PNFP-027 entered the open long-term extension study. Patients who had been on placebo in the original double-blind study were transferred to pioglitazone (roll-over placebo group) whilst those originally on pioglitazone continued on this therapy (roll-over pioglitazone group). 81 of these had previously received pioglitazone (+ metformin) and 73 placebo (+ metformin). 108 patients were followed for ≥ 48 weeks and 96 up to 72 weeks. The decrease in HbA<sub>1c</sub> was maintained for up to 72 weeks and the last observation carried forward (LOCF) analysis suggests only a small effect due to drop outs. Phase I and II studies indicate that pioglitazone has an effect on FBG within 2 weeks and on HbA<sub>1c</sub> after 8 weeks and that both effects plateau by 14-16 weeks.

While there are no long-term controlled trials available in combination, from the controlled and observational data it is likely that the efficacy of the pioglitazone + metformin combination would be maintained after 40 weeks.

#### Supportive studies

An open trial was performed in combination with voglibose (alpha glucosidase inhibitor). The trial results contribute to the safety database.

#### **Subsequent applications**

In a subsequent application (January 2003) the MAH submitted additional data on the use of pioglitazone as monotherapy and to increase the maximum daily dose to 45 mg. To support this a programme of four long-term studies (Quartet studies) has been conducted by the MAH. The Quartet studies have addressed and compared the magnitude and sustainability of the anti-hyperglycaemic effect over one year, both in monotherapy and combination therapy using doses of pioglitazone between 15 and 45 mg. In monotherapy pioglitazone has been compared with metformin and gliclazide. In combination therapy pioglitazone has been compared to the combinations of metformin + SU and metformin + gliclazide.

The Quartet studies involved 3713 patients, 1857 of which received pioglitazone.

In monotherapy studies type 2 patients (aged ≥ 35 and ≤ 75yr, C-peptide ≥ 1.5ng/ml) inadequately controlled by diet alone with HbA<sub>1c</sub> ≥ 7.5% and ≤ 11% were included. In combination therapy studies type 2 patients (aged ≥ 35 and ≤ 75 years, C-peptide ≥ 1.5ng/ml) inadequately controlled by SU or metformin alone respectively were entered into studies.

In addition supportive data from a further 1961 patients who received pioglitazone in shorter-term studies have been included in the type II variation and line extension applications of January 2003. Safety data from exposure on the market was estimated to be over 3 million patients amounting to just under 2 million patient years

### Efficacy endpoints

The primary efficacy endpoint in all trials was the change in HbA<sub>1c</sub> from baseline to endpoint using a Diabetes Control and Complications Trial (DCCT) traceable assay at a central laboratory.

Secondary endpoints included fasting plasma glucose (FPG) and fasting insulin. Effects on the lipid profile were investigated by measuring triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol (calculated according to the Friedewald formula) and calculating the total cholesterol:HDL cholesterol ratio.

### *Results*

Pioglitazone as monotherapy was shown to be statistically non-inferior to both metformin and gliclazide with respect to HbA<sub>1c</sub> reduction after one year of treatment. The mean reductions in HbA<sub>1c</sub> and FPG of 1.3-1.5% and 2.0-2.5mmol/l respectively, were maintained to a large degree at 12 months with pioglitazone and metformin, while gliclazide showed some fall-off. The percentage of patients reaching HbA<sub>1c</sub> values of  $\leq 7\%$  after one year from a mean baseline of 8.7% was comparable between the treatments (pioglitazone: 52-53%, metformin 53%, and gliclazide 47%). The proportion of patients showing response defined as HbA<sub>1c</sub> reduction from baseline  $>0.6\%$  was also similar, (pioglitazone: 79%, metformin: 78%; and gliclazide: 76%). The mean change in FPG (2.5mmol/approx) was significantly greater for pioglitazone than for either gliclazide or metformin (2.0-2.2mmol/l approx.).

In the analysis of the results of the combination studies by two-sided t-test, no treatment showed superiority over the other. After one year of combination therapy with either metformin or SU, pioglitazone showed no statistically significant difference with respect to the reduction in HbA<sub>1c</sub> from comparators.

Gliclazide added to metformin appeared to cause the most substantial loss in glycaemic control during the second half of the study.

The percentage of patients reaching HbA<sub>1c</sub> values of  $\leq 7\%$  after one year from mean baseline value of 8.5-8.8% was comparable between the treatments (pioglitazone: 35-39% (the higher value in combination with SU), metformin 40%, and gliclazide 35%). The proportion of patients showing response (defined as HbA<sub>1c</sub> reduction from baseline  $>0.6\%$ ) was pioglitazone: 67-70% (the higher value in combination with SU), metformin: 75%; and gliclazide: 63%.

Pioglitazone in addition to metformin or SU reduced fasting insulin levels. Metformin reduced insulin to a lesser extent in both settings, whereas gliclazide increased insulin levels.

Pioglitazone as monotherapy or in addition to metformin or SU respectively reduced fasting insulin levels. Metformin reduced insulin to a lesser extent in both settings, whereas gliclazide increased insulin levels

On the basis of the data from the Quartet studies it can be concluded that pioglitazone in doses up to 45mg whether used as monotherapy or in combination therapy improves glycaemic control in type 2 diabetes patients with similar efficacy as the currently accepted agents (metformin and SU). The data from the Quartet studies are satisfactory, although until outcome study results become available the long-term benefits of therapy with pioglitazone have not been demonstrated. The mean prescribed doses of pioglitazone (37-43mg), metformin (2124- 2074mg) and gliclazide (198-212mg) were reflective of the doses prescribed clinically. Glucose tolerance testing indicated that pioglitazone may improve post-prandial glycaemia. In these patients the reduced post-prandial glucose excursions were associated with little change in insulin levels. Pioglitazone also improves the HDL : total cholesterol ratio to at least the same extent as metformin. In addition, pioglitazone reduced the urinary albumin:creatinine ratio by 10-20% in combination therapy.



### **Discussion on clinical efficacy**

Pioglitazone monotherapy decreased HbA<sub>1c</sub> and FBG significantly as compared to placebo with concomitant reductions in fasting C-peptide and insulin. Triglycerides were reduced. In most studies, HDL-cholesterol increased (+4 to 11%) and LDL-cholesterol was either increased or unchanged (mean effect +0.2 to 7.8 %). ApoA1 was not measured and HDL/TC ratio was not provided, however calculated HDL/TC ratios show an increase of 5-10% with pioglitazone. Blood pressure did not change.

In combination, pioglitazone was added to insulin, SUs, and metformin respectively, in placebo controlled studies.

The data from the Quartet studies are satisfactory, although until outcome study results become available the long-term benefits of therapy with pioglitazone have not been demonstrated.

### **Clinical safety**

#### **Patient exposure**

Overall, 5509 patients took part in clinical studies out of which 4339 were exposed to pioglitazone: 2665 in European and US trials, 1118 in Japanese trials and 556 in clinical pharmacology studies. Doses of 7.5 mg to 60 mg have been administered. At the time of submission, the average duration of exposure in European and US studies was 39 weeks. Updated safety data are available for pioglitazone + SU in over 600 patients from double- and single-blind, placebo-controlled trials and over 400 patients in open label trials of whom 278 received the combination for at least one year. For pioglitazone + metformin 168 patients are available from double-blind placebo-controlled trials and 154 from open label trials of whom 100 received the combination for one year or longer. More than 152 patients received pioglitazone + sulphonylurea for at least 72 weeks, 96 received pioglitazone + metformin and 199 pioglitazone + insulin.

Safety was assessed on the following criteria: vital signs and physical examination, body weight, blood pressure, and the collection of adverse events (AEs), serious AEs, routine laboratory safety tests, urine cytology, chest X-ray, ECGs and in some studies echocardiograms.

Total exposure to pioglitazone consists of about 2600 patient-years in the trials supporting the monotherapy and 45 mg application (January 2003), 1000 patient-years from the previously submitted studies and about 1.8 million patient-years from the market.

#### **Adverse events**

The summary of cumulative 12-week incidence rates (95 % confidence intervals) for the most common adverse events during double-blind treatment period in the US and European controlled monotherapy studies submitted in the original MAA is shown in Table 8.

Table 8: AEs occurring in >2 % of patients and more frequently with pioglitazone

WHOART	Placebo (n=431) (95 % CI)	Pioglitazone (n=862) (95 % CI)
At least 1 AE except hyperglycaemia or diabetes aggravated	57.0 (52.1-61.9)	59.7 (56.2-63.1)
Upper respiratory tract infection	7.2 (4.6-9.8)	8.7 (6.7-10.6)
Headache	6.5 (4.0-9.0)	7.0 (5.2-8.8)
Sinusitis	2.9 (1.2-4.7)	3.6 (2.3-5.0)
Myalgia	2.3 (0.7-3.9)	3.2 (2.0-4.5)
Oedema	0.6 (0.0-1.4)	3.2 (2.0-4.5)
Back pain	2.3 (0.7-3.8)	3.1 (1.9-4.3)
Urinary tract infection	1.6 (0.3-2.9)	2.7 (1.6-3.9)
Pharyngitis	0.3 (0.0-0.8)	2.7 (1.6-3.9)
Tooth disorder	1.5 (0.3-2.6)	2.6 (1.4-3.7)
Fatigue	2.4 (0.8-4.0)	2.5 (1.4-3.6)
Accidental injury	1.5 (0.3-2.8)	2.2 (1.2-3.2)
Cramps legs	1.1 (0.0-2.1)	2.1 (1.1-3.2)
Vision abnormal	1.4 (0.2-2.6)	2.1 (1.1-3.1)

- Oedema

Oedema occurred more commonly with pioglitazone than placebo and the investigators considered it as “related” more often. Oedema appears to be a dose-dependent phenomenon with pioglitazone. Oedema has only rarely caused patients to withdraw from clinical studies, and was not related to reporting of right or left ventricular failure, shortness of breath or angina, although patients with Class III and IV cardiac failure have not been included in these studies. Patients >65 years in general had similar adverse events to those younger, and at similar frequency, however peripheral oedema was reported slightly more frequently in the elderly (5.8% vs. 2.6%). Peripheral oedema was more common in females (5.9%) than in males (1.2%).

In combination trials, oedema and peripheral oedema were increased in combination therapy insulin+pioglitazone (15.6% vs. insulin+placebo 7.5%), in metformin+pioglitazone (6.0% vs. 2.5% metformin + placebo) and SU+pioglitazone (7.5% vs. 2.1% SU+ placebo).

In the combination pioglitazone + metformin study there was no increased use of diuretics by comparison with metformin and placebo.

No symptomatic hypoglycaemia (confirmed with measurement of blood glucose) occurred in patients receiving pioglitazone alone or placebo.

Combination therapy in general showed a similar adverse event profile to monotherapy. However, sulphonylurea and insulin combination groups reported hypoglycaemia, in particular the insulin combination group (11.6 % vs. 4.8 % in placebo). Metformin combination did not show any increase in hypoglycaemia over metformin alone.

Overall, small decreases in haemoglobin, haematocrit and red cell count have been seen in monotherapy and combination therapy. The changes are similar in the long term studies. Changes in haemoglobin were attributed to haemodilution.

A higher incidence of myalgias, leg cramps or pain was reported in the pioglitazone groups. Increases in LDH (by approximately 10 %) and CPK (by approximately 15 %) compared to placebo were seen in monotherapy studies, but not related to clinical signs. Similar LDH and CPK changes are seen in combination therapy, and in the long-term studies. The changes were usually transient and normalisation occurred despite continuing pioglitazone, and there was no changes observed in relation to combined lipid-lowering agents. In placebo-controlled trials changes in CPK were lower in patients treated with statins together with pioglitazone than in those treated with pioglitazone alone. 1.1% of patients in controlled studies and 4.2% in long term studies had CPK > 3ULN and were taking

pioglitazone + statins while 1.8% and 2.8% respectively had CPK > 3ULN and were taking pioglitazone without statins.

Approximately the same number of patients taking pioglitazone as that taking placebo took statins (11%). Approximately 17% of patients were taking statins in the long-term studies.

#### Serious Adverse Events and Deaths

In double-blind studies in Europe and US 3 % of patients on pioglitazone reported a SAE, compared with 4.2% on placebo. These were mainly cardiovascular events.

In open, long term studies, overall 8.1 % of patients had a SAE (excluding loss of diabetic control). These were mainly cardiovascular, neoplastic and musculo-skeletal in nature. There was no underlying pattern of events.

On combination therapy, SAEs were reported in 4.2-6.1% of patients, except in the metformin + placebo group, in which 1.3% were reported. Again there was no pattern emerging from the underlying causes of these SAEs.

SAEs judged attributable to study drug occurred in 3 pioglitazone-treated patients and 1 placebo-treated patient in monotherapy studies.

There was 3 deaths in the pioglitazone and 4 in placebo group; there was no indication of excess mortality for pioglitazone.

#### Discontinuation due to adverse events

Withdrawal rates due to adverse events were similar in pioglitazone and placebo treated groups, the global incidence was 8.9 %.

#### Safety in special populations

##### Adverse events in elderly

Adverse events were compared in the <65 years old and ≥ 65 years old patients. No difference was found except for oedema that was more frequent in pioglitazone-treated elderly than placebo-treated elderly patients.

#### Discussion on clinical safety

- Decreases in haemoglobin and anaemia

Decreases in haemoglobin were reported, which were attributed to fluid retention (as shown by oedema occurrence). The study performed to investigate fat distribution actually showed no change in body water. However, no specific studies have been performed to investigate the proposed mechanism.

##### Oedema

Oedema was one of the most frequent adverse events reported with pioglitazone. It was dose dependent and occurring more frequently when pioglitazone was used in any of the combination therapy.

- Cardiac Safety

Blood pressure did not change appreciably in any of the clinical studies.

QT<sub>c</sub> intervals have been measured in many studies, and no changes have been observed in man after treatment with pioglitazone.

In relation with preclinical findings and clinical findings (oedema), there were concerns that pioglitazone might produce cardiac hypertrophy and heart failure in diabetic patients (at-risk population). Very few cases of heart failure were reported in clinical trials or post marketing. No statistically significant difference with the placebo group in controlled trials has been found. In the combination trial of insulin with pioglitazone, more patients in the pioglitazone group took diuretics.

Echocardiography (M-mode, centrally read) has been used to assess left ventricular mass index (LVMI) with pioglitazone (open label PNFP-011). There has been no clinically significant change in LVMI seen

in the programme but the size of the population studied is considered too limited (about 250 patients at week 48 with an additional 107 patients at week 108 and 60 at week 132). No functional parameters (for early detection of cardiac abnormality) were recorded.

- Body Weight

Pre-clinical studies have shown body weight to increase in animals.

In man, a detrimental effect of weight gain on the cardiovascular system is possible with a cycling effect resulting in greater obesity. Obese individuals develop cardiovascular disease more frequently than the non-obese and there is a particular risk of ischaemic heart disease in those with a central distribution of obesity.

In controlled pioglitazone monotherapy studies, a mean weight gain of 1.4 kg and 3.0 kg (in European and US trials, respectively) was seen using up to 45 mg pioglitazone. The weight gain was greater when pioglitazone was used in combination with SU or insulin. Weight increase resulted in 7 patients in dose ranging studies (PNFP-001), and 2 patients on pioglitazone+insulin combination discontinuing treatment (one patient had a 10-kg weight increase in 21 days, the second mild weight gain with fluid retention, both cases were judged possibly related). In long-term studies an increase in weight was seen with pioglitazone monotherapy, averaging 5.5 kg over a year.

To address the question regarding the nature of the weight gain, a European Body Composition Study (18-week trial: 45 mg monotherapy vs. placebo) was undertaken. The study indicated that the weight gain following pioglitazone HCl was composed of fat. There was a significant decrease in intra-abdominal (visceral) fat while extra-abdominal fat increased.

The Body Composition Study showed no significant change in total body water and the intravascular volume study in healthy volunteers showed no significant fluid accumulation.

Through a type II variation section 5.1 “Pharmacodynamic properties” of the Summary of Product Information has been updated to include the results of this study.

The weight increase has been shown in a controlled study with pioglitazone and SU to be primarily related to increases in fat body mass (MRI study) with a subcutaneous distribution rather than an increase in visceral fat. This study also demonstrated no change in total body water, although clearly to explain peripheral oedema and haemoglobin changes some water retention does occur.

The mean increase in weight at 72 weeks of treatment was approximately 5 kg for both the metformin+pioglitazone 30 mg and SU+pioglitazone 30 mg combination. This increase was at least double that noted at 12-16 weeks in the controlled studies. Although the weight gain seems to have plateaued between 24 and 60 weeks, it nonetheless is a substantial weight gain in a US population whose mean baseline BMI was of the order of 32 kg/m<sup>2</sup>. The weight gain achieved in the SU + pioglitazone combination studies from Japan was approximately half this amount.

The need for monitoring weight and controlling diet has been mentioned in the SPC.

- Liver toxicity

There was a particular concern with liver toxicity as another thiazolidinedione has been associated with serious liver toxicity.

No liver toxicity from pioglitazone was seen in the toxicology studies.

In monotherapy studies fewer patients developed liver function tests  $\geq 3$ ULN with pioglitazone than on placebo. No patient developed liver function tests  $\geq 10$ ULN.

In the long-term studies, one patient had a markedly abnormal bilirubin, and subsequently died from cholangiocarcinoma. One further patient had abnormal liver tests at baseline, but this returned to normal on treatment with pioglitazone.

In the combination studies, there are ten reports of markedly abnormal liver tests ( $>3$ ULN) on pioglitazone (nine of which were in combination with insulin), and 12 instances on placebo with concomitant anti-diabetic therapy (four of these were on insulin).

There is a 0.4% reporting rate for liver and hepatobiliary adverse events on both pioglitazone and placebo. Of those patients who had abnormal liver function, many had other hepatobiliary disorders such as cholecystitis or pancreatic malignancy.

In controlled monotherapy studies three hepatobiliary serious adverse events were seen. Of the two on pioglitazone, one had cholelithiasis and the other had carcinoma of the pancreas. There were three serious adverse events on long term, open label treatment also related to cholelithiasis (two) and cholecystitis (one). A further patient had a cholangiocarcinoma categorised.

There were five hepatobiliary serious adverse events in combination studies, all on pioglitazone, and these all related to cholelithiasis or gall bladder disorder. There were no product-related deaths from hepatobiliary disease.

- Urine cytology

Follow up of patients (including urine cytology and if positive appropriate further investigations) from the controlled US and the Japanese studies did not reveal any bladder malignancies.

- Colon cancer

No signal of an increased risk of malignancy has been detected in clinical trials with pioglitazone. It has been shown that PPAR- $\gamma$  is expressed in tumour cell lines, and that troglitazone and rosiglitazone may promote colon tumours in transgenic mice. No increases in colon tumours were seen in rat or mouse carcinogenicity studies with pioglitazone.

There is a concern with the use of thiazolidinediones in patients with an increased risk of colon cancer (e.g., familial colon polyposis). This concern is addressed in the Preclinical Safety Data section of the SPC.

The post-hoc analysis of safety (and efficacy) results in the subset of diabetic population where there might be an unmet medical need, i.e., the patients insufficiently controlled on SU but who cannot tolerate metformin (this analysis was requested by the CPMP) did not reveal specific concerns. The safety profile in this subset of patients was comparable to that of the overall population.

## **Conclusion**

There is no evidence from clinical studies of pioglitazone causing liver dysfunction. Although oedema occurred in a significant number of patients, no cardiovascular safety signal was identified in the short term. In the long term, there are insufficient numbers of patients to fully assess the potential cardiovascular risks in this population. This would need to be further investigated in clinical trials with both efficacy and safety endpoints. The occurrence of substantial weight gain is a cause for concern particularly in a population where obesity is so prevalent.

The Quartet studies demonstrated that pioglitazone in doses up to 45 mg in monotherapy and in combination therapy did not reveal new or unexpected adverse events. However CPMP noted that these studies are efficacy studies. They can be supportive for the safety of pioglitazone but cannot provide conclusive evidence of safety. Therefore there is still a need to have more data from post-marketing studies with regards to the cardiovascular safety profile of pioglitazone.

## **5. Overall conclusions, benefit/risk assessment and recommendation**

### **Quality**

The pharmaceutical documentation showed the quality of the product was acceptable.

### **Preclinical pharmacology and toxicology**

Pioglitazone is a thiazolidinedione compound acting as a PPAR $\gamma$  agonist to reduce hyperglycaemia and possibly insulin resistance.

Pioglitazone has been shown to be devoid of genotoxic potential in a standard battery of tests. Pioglitazone was not carcinogenic in mice. A safety concern was identified in rat preclinical studies where bladder hyperplasia were observed in both sexes, and tumours in males only at plasma levels close to human exposure. A case control study will be performed investigating this issue post marketing.

### **Efficacy**

Pioglitazone has been shown to cause a statistically and clinically significant reduction in HbA<sub>1c</sub> and glucose (FBG and post-prandial AUC) in doses of 15-45 mg in patients with type2 diabetes.

Simultaneously there has been a reduction in fasting insulin, a decrease in triglycerides and a rise in HDL and inconsistent though mainly non-significant versus placebo changes in LDL.

#### *Monotherapy*

The clinical efficacy of pioglitazone in monotherapy was considered insufficiently documented as compared to available anti-diabetic medicinal products, i.e., sulphonylureas. There was no comparison with metformin, which is an insulin sensitiser. The population included in the trials was heterogeneous, including both naive and previously treated diabetic patients, and patients with a wide range of BMI. The duration of controlled trials was considered too short for a full efficacy and safety assessment, especially in the context of chronic use as expected in diabetes. Long-term open trials were not controlled.

#### *Combination therapy*

The clinical efficacy of pioglitazone in combination with other anti-diabetic medicinal products has not been compared to the widely-used sulphonylurea+metformin combination.

In combination with metformin, short-term efficacy data with pioglitazone are considered sufficient in obese patients not controlled on metformin alone. No long term trials are currently available for safety and efficacy, which in the context of a chronic disease such as type 2 diabetes is not sufficient.

As for monotherapy, the duration of trials was limited and considered insufficient for long-term use of the product.

The Quartet studies were undertaken to address the above concerns with regard to the monotherapy and combination therapy use of pioglitazone. The new data of the Quartet studies offers some reassurance, however the long-term benefits of therapy with pioglitazone have not yet been confirmed.

However, in clinical practice, there is an unmet medical need in a subset of patients in whom metformin is not tolerated or contraindicated. In this subset of patients, pioglitazone (15-45 mg) in combination with sulphonylureas may retain some benefits and the analysis of available data in this population shows that the efficacy is similar to that of the overall studied population.

#### **Safety**

The major clinical safety issues discussed by the CPMP during the assessment were liver toxicity, weight gain, and potential cardiac toxicity in relation to oedema. It was accepted that there is no signal for liver toxicity of pioglitazone in clinical trials.

Weight gain has been noted with pioglitazone monotherapy as well as combination therapy with insulin and SU, but not with metformin; weight gain is a concern in this often obese population.

At the time of the assessment, there were no long-term data available on potentially deleterious effects on cardiovascular disease, heart function, and insulin resistance. Long-term echocardiography data are only available in a limited subgroup of patients and long-term controlled clinical trials including cardiovascular safety endpoints were lacking in a population at high risk of cardiovascular disease. The absence of negative effects on blood pressure was considered as reassuring.

Due to the absence of long-term data, the overall effect of pioglitazone on cardiovascular risk cannot be assessed.

The studies included in the monotherapy and 45 mg applications (January 2003) did not reveal new or unexpected adverse events. The section 4.8 “Undesirable effects” of the SPC has been updated to reflect the adverse events related to the use of pioglitazone as monotherapy.

#### **Benefit/risk assessment**

The efficacy and safety of pioglitazone as monotherapy were not considered to be sufficiently demonstrated in the absence of a comparison with available reference treatments and long term controlled efficacy and safety data. The use of pioglitazone in patients with secondary failure with SUs has not been directly studied in the dossier and such an indication would need to be supported by specific efficacy and safety data.

The efficacy and safety of pioglitazone in combination with either insulin or sulphonylureas were not considered as sufficiently demonstrated in absence of long term controlled efficacy and safety data. In

particular, the pioglitazone-induced adverse effects such as weight gain and oedema were considered unacceptable. This has been addressed in the SPC by adding a contraindication to the use of pioglitazone in combination with insulin.

In addition, the CPMP recognised that there was no cardiovascular safety signal identified in the short term. However, the data provided were insufficient to provide reassurance on the long term, especially concerning the occurrence of heart failure in patients with NYHA I or II.

The CPMP considered that the current efficacy and safety data on the use of pioglitazone in combination with SUs were only acceptable in the population where there is an unmet medical need.

Among the patients insufficiently controlled on monotherapy with one of the currently approved oral antidiabetics, there is a subgroup of patients for whom the metformin+sulphonylurea combination is not an option. Currently the available therapy for these patients would be insulin, and insulin therapy is associated with practical problems in elderly patients as well as the risk of hypoglycaemia. Therefore, the use of pioglitazone (15-30 mg) can be recommended for specific subgroups of patients for whom an unmet medical need is described, especially those with insulin resistance. Specifically, on request from the CPMP, data were submitted to support the use of pioglitazone in combination with a sulphonylurea in patients who are not satisfactorily controlled upon monotherapy and show gastrointestinal intolerance to metformin or in whom metformin is contraindicated. Furthermore, data were submitted to support the use of pioglitazone in combination with metformin in obese patients who are not satisfactorily controlled upon metformin monotherapy. In discussing the timing of studies to address the potential cardiovascular risk, some CPMP members maintained that further safety studies should be performed prior to the marketing authorisation. However, the majority of the CPMP considered that, as the indication for pioglitazone has been restricted to patients with an unmet medical need, these studies could be undertaken as a post-marketing commitment. The Applicant has committed to perform adequate post-marketing studies to address the open safety issues. These studies will investigate the progression of CHF in type 2 diabetes patients treated with pioglitazone, and long-term effects of pioglitazone on lipids, and will compare combined therapy with pioglitazone to a combination of other anti-diabetic agents. In addition, further safety data will be collected from a case control study, and prescription event monitoring.

Based on data from the quartet studies, the CPMP recommended the increase of the approved daily dose of pioglitazone to 45 mg.

The data from the application to support the use of pioglitazone in monotherapy were satisfactory. However the CPMP considered that there are still unresolved concerns regarding long-term safety data for pioglitazone and lack of outcome data with thiazolidinediones. Therefore the CPMP was of the opinion that the monotherapy indication for pioglitazone should respect the first-line status of metformin, clearly indicating that pioglitazone is an alternative for patients for whom metformin would otherwise be the first alternative. The CPMP was also of the opinion that the use of pioglitazone in monotherapy should be restricted by using a weight qualification. The CPMP recommended the second-line monotherapy indication.

In order to harmonise the indication for combination therapy with the monotherapy indication, the weight qualification was subsequently amended from obese to overweight patients.

### **Recommendation**

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered that the benefit/risk profile of Actos was favourable for a restricted indication: “only in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated doses of oral monotherapy with either metformin or a sulphonylurea:

- in combination with metformin only in obese patients,
- in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated”.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered that the benefit/risk profile of Actos was favourable in the following therapeutic indications:

“as oral 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.

Pioglitazone is also indicated for oral combination treatment in type 2 diabetes mellitus patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or sulphonylurea:

- in combination with metformin particularly in overweight patients
- in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated”