SCIENTIFIC DISCUSSION

1. Introduction

Type 2 diabetes mellitus is a heterogeneous disorder characterised by multiple defects in the pancreatic β-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 prolonged hyperglycaemia, which results from the metabolic defects causes microvascular and macrovascular damage, which is a cause of considerable morbidity and mortality.

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. The main goal of treatment for type 2 diabetes is to prevent acute and chronic complications, through better control of blood glucose levels and the management of macrovascular risk factors associated to diabetes (dyslipidaemia, blood pressure control and central obesity). The Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS) demonstrated that HbA_{1c} must be reduced to <7% to minimise the development of microvascular complications. 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 (Met), which 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.
- Thiazolidinediones (TZDs), such as pioglitazone, which increase insulin sensitivity and enhance glucose uptake in skeletal muscle.
- Alpha-glucosidase inhibitors, which have shown limited efficacy but with no risk of hypoglycaemia. Gastrointestinal undesirable effects limit compliance.
- Insulin, which is used in type 2 diabetes 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 ≤ 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.

Within 3 years of onset of type 2 diabetes, approximately 50% of patients require multiple therapy, and after nine years this number increases to 75%. Current guidelines recommend the addition of SU

as first line combination with metformin but there is evidence that clinicians are adopting thiazolidinediones as the second treatment to add to metformin (before SU) in an attempt to preserve pancreatic function.

Compliance with treatment is an important factor in achieving glycaemic control. The combination of two different classes of antihyperglycaemic agents in a single tablet can simplify the treatment and serve to improve compliance.

Currently, SU-metformin FDC are not available on the European market. In October 2003, a fixed dose combination of rosiglitazone-metformin was approved through the centralised procedure with the indication "Treatment of type 2 diabetes mellitus patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone".

This application was for a fixed dose combination product, Competact, containing two authorized ingredients, pioglitazone hydrochloride and metformin hydrochloride.

Pioglitazone (as hydrochloride) (Actos; Glustin) was originally authorized in the European Union in October 2000 at doses of 15 or 30 mg once daily 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 SU only in patients who show intolerance to metformin or for whom metformin is contraindicated."
In 2002, new data were submitted in a type II variation and pioglitazone was approved for "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." In a subsequent type II variation, the approved maximum daily dose was increased to 45 mg. At this time, the application for an unrestricted combination therapy (i.e. deleting current qualifying conditions for its use in combination with metformin or SU) was rejected by the CHMP.

Metformin was originally granted national authorisations in the EU from 1959 to 1997. Following a referral to the CPMP under Article 11 of Council Directive 75/319, as amended, a decision on a harmonised SPC for metformin was issued in February 2001. The indication proposed for Competact is consistent with that already approved for Actos in combination with metformin.

This application was submitted under Part B of the Annex to regulation 2309/93 and was a full "mixed" application in accordance with Article 8(3) and Annex I Part II.7 of Directive 2001/83/EC as amended.

The present application for a fixed-dose combination was based mainly on:

- Three already assessed clinical studies where pioglitazone was added to metformin and that previously supported the approval of the product to be used in combination with metformin .
- New clinical pharmacology studies intended to demonstrate that the FDC tablet is equivalent to both tablets taken separately.

2. Quality aspects

Introduction

The product is a fixed dose combination containing 15 mg of pioglitazone (as hydrochloride) and 850 mg of metformin hydrochloride as active substances. They are presented as film coated tablets.

Other ingredients are: cellulose microcrystalline, povidone, croscarmellose sodium, magnesium stearate, hypromellose, macrogol, talc, and titanium dioxide.

Film coated tablets are supplied in aluminium/aluminium blisters.

Active Substances

Two active substances are used in this fixed combination product, pioglitazone hydrochloride and metformin hydrochloride.

Pioglitazone (as hydrochloride)

This active substance has been authorised as a result of an earlier centralised procedure for the same applicant under the invented names Actos (EU/1/00/150) and Glustin (EU/1/00/151).

It is a white crystalline solid that is odourless and slightly bitter. The active substance is produced as a racemate and it is practically insoluble in water; from practically insoluble to sparingly soluble in aqueous solutions at different pH values, it is soluble in several polar organic solvents and freely soluble in dimethylsulfoxide. Pioglitazone hydrochloride has a specific crystalline form and has not demonstrated polymorphism.

Pioglitazone HCl is manufactured, by chemical synthesis, in five steps. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents, have been presented. The three batch synthesis data for each manufacturing site presented show a reproducible manufacturing process leading to homogeneous batches.

Pioglitazone hydrochloride specifications includes tests for description, identification (IR, UV and HPLC), assay (HPLC, 99.0-101.0%), related substances (HPLC), residual solvents (GC), water content, residue on ignition, heavy metals, and particle size.
The tests and limits in the specifications are considered appropriates for controlling the quality of this active substance.

The re-test period proposed is acceptable according to the stability data submitted.

Metformin hydrochloride

Metformin hydrochloride described in the Ph. Eur. It is a white crystalline powder that is odourless and has a slightly bitter taste. The compound is hygroscopic, freely soluble in water, slightly soluble in alcohol and practically insoluble in acetone, ether and chloroform. It has a specific crystalline form and has not demonstrated polymorphism. Particle size does not influence dissolution of metformin hydrochloride, because it is freely soluble in water.

The chemistry, manufacturing and control information on metformin hydrochloride has been evaluated by the EDQM and a European Certificate of Suitability of the Monograph of the European Pharmacopoeia (CEP) has been issued. No additional tests are included in the CEP.

Metformin hydrochloride specifications includes tests for description, identification (IR, PhEur), solubility (Ph Eur), melting point (Ph Eur), Loss on drying (Ph Eur), heavy metals (Ph Eur), content (Ph Eur, 98.5-101.0%), impurities (HPLC), residual solvents (GC), and particle size.

The tests and limits in the specifications are considered appropriates for controlling the quality of this active substance.

Batch analysis data of the three batches of metformin hydrochloride active substances are provided. The three lots are within the specifications and consistent from batch to batch.

The stability of metformin hydrochloride active substance has been evaluated for 19 batches storaged under 25ºC ± 2ºC / 60% ± 5% up to 60 months and under 40ºC ± 2ºC / 75% ± 5% for 2 batches.

The re-test period proposed was considered acceptable according to the stability data submitted.

Medicinal Product

- Pharmaceutical Development

As the product is a combination of two existing oral antidiabetics, the product was developed to be bioequivalent to commercial products containing the individual active substances. It was found that the two most important properties to influence the formulation selection were the dependence of pioglitazone hydrochloride solubility on pH and the marked increase in pH occurring with the dissolution of metformin hydrochloride thereby affecting pioglitazone hydrochloride solubility. Therefore, particle size of pioglitazone hydrochloride played an important factor in the drug formulation development. The reduced particle size of pioglitazone hydrochloride allows its dissolution at an acidic pH before the dissolution of metformin hydrochloride changes the pH to an alkaline pH.

To investigate the potential for interactions between the active substances and other ingredients that might be used in tablet formulations, the binary compatibility of pioglitazone hydrochloride and metformin hydrochloride with each other and the excipients used for the medicinal product dosage forms was studied using stress and accelerated conditions. Both active substances and each excipient were mixed physically at an appropriate ratio. Good compatibility was demonstrated between all of them.

In order to avoid the metformin hydrochloride unpleasant taste, the medicinal product has been developed as film-coated tablets. The excipients are conventional and compatible with the active substances, and meet the requirements in Ph. Eur.
The excipients used are: cellulose microcrystalline (diluent), povidone (binder), croscarmellose sodium (disintegrant), magnesium stearate (lubricant), hypromellose (film coating agent), macrogol (plasticizer), talc (lubricant), and titanium dioxide (pigment). There are not excipients of animal or human origin.

The package selected for tablets is a conventional blister aluminium/aluminium, that is a protective container against moisture. The choice of container is influenced by the hygroscopic properties of metformin hydrochloride and thus the formulation itself. Stability studies demonstrated the suitability of the chosen package.

- Manufacture of the Product

Product manufacture consists of standard processes including mixing/pulverisation, granulation/ milling, blending, compression, and film coating.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process in three production-scale batches of each and is satisfactory. The in process controls are adequate for this film coated tablet preparation.

The 6 commercial scale batch analysis data provided show that the film coated tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

- Product Specification

The product specifications include tests by validated methods for appearance, identification of the active substances (HPLC, UV), dissolution of the active substances (Ph Eur), uniformity of content of the active substances (HPLC), assay of the active substances (95-105%, HPLC), related substances (HPLC), and microbial limit (Ph Eur).

Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.

The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.

Batch analysis data on three pilot-scale batches confirm satisfactory uniformity of the product at release.

- Stability of the Product

Stability data of three pilot batches of both strengths stored for 6 months at 40˚C ± 2˚C/75% RH ± 5% RH and for 18 months at 25˚C ± 2˚C/60% RH ± 5% RH were provided. In addition, samples were stored in stress conditions at 50ºC for 3 months; 60ºC for 2 months, 25ºC/31%RH and 25 ºC/93 % for 3 months and were also exposed to light

The batches of tablets were packed in the primary packaging proposed for marketing. Samples were tested for appearance, dissolution, assay, related substances, hardness, loss on drying (LOD), microbial testing and moisture limits.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Bioequivalence

Biopharmaceutics studies demonstrated bioequivalence of both doses of the fixed combination product to the individual commercially available pioglitazone and metformin products. Efficacy and safety of the combination product is based on studies of concomitant administration of the two drugs and on postmarketing experience. As bioequivalence has been demonstrated, the product is expected to be as safe and effective as the concomitant use of the individual drugs. See clinical part of the report for details.

Discussion on chemical, pharmaceutical and biological aspects

In general, the quality of the product is adequately established, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. Relevant ICH/CPMP guidelines and Pharmacopoeial requirements have been taken into account in the quality documentation and there are no major deviations from EU and ICH requirements.

Two active substances are presented in this fixed combination: pioglitazone and metformin hydrochloride. Pioglitazone data were originally presented in a previous EC application dossier relative to pioglitazone tablets, and information on metformin hydrochloride has been supplied in the form of a CEP.
Acceptable specifications have been presented for both active substances. The synthetic pathway, the structure and impurity profile are characterized and are in line with current ICH guidelines. The stability data on the active substances supports the proposed re-testing period.

The development and the manufacturing process of the finished products are properly described, the results from validation batches show that the manufacturing process is successfully validated, and are suitable to ensure consistent quality of the active substance and the finished product.
Based on available stability data, the proposed shelf life stated in the Summary of Product Characteristics can be accepted.

3. Non-clinical aspects

Introduction

No new non-clinical studies were conducted by the applicant with the FDC (fixed dose combination) compound. The applicant has submitted extensive documentation concerning nonclinical pharmacology, pharmacokinetics and toxicology of pioglitazone and metformin.

The nonclinical data relating to pioglitazone is derived from bibliographic references and original data of the previous pioglitazone submission made in 1999.
The applicant has performed an extensive literature review on metformin using the dates 1960 to 2005 to search pubmed and toxnet with applicable search terms. There is a paucity of non-clinical studies on metformin (especially related to pharmacokinetics and toxicology), but this is superseded by long-term clinical experience.
In view of the length and extent of clinical experience obtained with co-administration of commercially available pioglitazone and metformin, the absence of additional non-clinical studies was considered acceptable.

All pivotal pioglitazone non-clinical studies were conducted according to GLP. Non-clinical studies of metformin were conducted prior to the establishment of GLP criteria.

Pharmacology

- Primary pharmacodynamics

In vitro, pioglitazone shows high binding affinity for activating the human and rat PPARγ (EC50 ranging from 420 to 680 nmol/L), but only weak activation of the human PPARα. Metabolites (M-II, M-III and M-IV) of pioglitazone showed also activity on PPARγ. In vivo, pioglitazone reduced tumour necrosis factor α and sphingomyelinase (thought to play a role in the development of insulin resistance) levels in the tissues of insulin resistant rats to values comparable to those found in insulin-sensitive rats. Increased insulin-stimulated glucose incorporation, glycogen synthesis and glycolysis were observed in preparations from animals treated with pioglitazone. Pioglitazone had no effect on plasma glucose or insulin in normoglycemic rats, but induced dose- and time-dependent reductions of plasma glucose, insulin, triglycerides, and non-esterified fatty acids elevations in insulin-resistant, genetically obese/hyperglycaemic rodents. Pioglitazone improved fasting and postprandial serum immuno-reactive insulin and dose-dependently decreased plasma glucose and triglycerides in spontaneously obese monkeys, but effects on obese beagle dogs were not consistent. Metabolites M-II, M-III and M-IV showed lower but significant hypoglycaemic and hypotriglyceridemic activities.

The mode of action of metformin is not fully understood, but recent experimental evidence shows that metformin decreases gluconeogenesis. In vitro, metformin increases the functional activity of glucose transporters (GLUT-1 and GLUT-4), stimulates AMPK activity, and inhibits glucose-stimulated insulin secretion in both human pancreatic islets and a β-cell line (MIN6). In vivo, metformin increased glycogen synthase and glycogen phosphorylase in the liver in diabetic mice and controlled glycaemia in naturally acquired diabetic cats for 4 months. However, in conscious normal dogs the primary effect on glucose metabolism was attributable to a decrease in hepatic glycogenolysis and not to an alteration in gluconeogenic flux.

Coadministration of pioglitazone and metformin decreased plasma glucose and insulin levels further than both drugs separately, but did not result in additional decreases of plasma TG levels.

- Secondary pharmacodynamics

The distribution of white and brown adipose tissue is modulated by pioglitazone. Increases in white fat depots result from increased caloric intake when the animals are fed *ad libitum* but can be controlled by restricting food intake. Human adults do not have an equivalent tissue to the brown fat deposits found in rodents thus there can be no clinical impact of the effect of pioglitazone on brown fat. Since the animal studies show that dietary restriction can prevent weight gain as a result of increased white fat deposition, dietary control should form part of patient treatment.
Studies in models of type II diabetes in mice, rats, and dogs showed that metformin has vasculoprotective effects. Anti-ischemic effects have been demonstrated in non-diabetic hamsters, rats, and humans. The beneficial effects in both diabetic and non-diabetic subjects indicate that the effect is independent of the antihyperglycaemic activity of metformin. Several mechanisms appear to be involved.

- Safety pharmacology programme

A series of general pharmacology studies were carried out to test the potential of pioglitazone to alter cardiovascular, respiratory, central nervous and gastrointestinal system function. In mice, pioglitazone decreased spontaneous locomotor activity and showed no effects on skeletal muscle coordination or on pentobarbital-induced sleep time; there were no pioglitazone-related effects on body temperature and spinal reflex in rats or abnormal activity on EEG recorded from cats. Pioglitazone did not affect the blood pressure or heart rate in conscious rats or beagle dogs at a dose of 300 and 30 mg/kg. Recent studies suggest that pioglitazone had no significant effect on ventricular myocyte excitability, action potential configuration, or membrane currents over the concentration range 1 to 10 µmol/L. At 100 µmol/L, pioglitazone produced a rightward shift in the concentration-response curve of the contraction of the isolated guinea pig ileum in response to acetylcholine, histamine, and barium and slightly inhibited the maximum contraction. Pioglitazone had no significant effect on gastric emptying, intestinal transport, and urine volume or urinary excretion of sodium or potassium in rats.

No formal safety pharmacology studies have been performed on metformin that was developed in the 1950s. No such studies are considered necessary in view of the extensive clinical experience accumulated over several decades of use.

- Pharmacodynamic drug interactions

No specific studies of potential drug interactions with pioglitazone were carried out. The weight of evidence suggested that serious adverse drug interactions with insulin, glibenclamide or voglibose, an α-glucosidase inhibitor, were unlikely. No specific studies on the safety pharmacology of metformin were provided, which was acceptable as it is superseded by clinical experience.

Pharmacokinetics

Pioglitazone is a high permeability and low solubility drug, metformin is a low permeability and high solubility drug, good absorption was observed in animals and in humans for both drugs with no (metformin) or low (pioglitazone) hepatic first-pass effect.

Plasma protein binding of pioglitazone across species was relatively high. Radioactivity was widely distributed to tissues in rats after [^{14}C]pioglitazone administration, and was excreted into milk of lactating rats. Metformin binds negligibly to plasma proteins.

Pioglitazone did not induce cytochrome P450 in rats. All six human Phase I metabolites of pioglitazone were identified in mice, rats, dogs, and monkeys. Pioglitazone is metabolized primarily by CYP2C8 and CYP3A4. The contribution of these CYP isoforms to the metabolism of pioglitazone was comparable with the residual activity caused by other isoforms including CYP1A1, CYP1A2, CYP2C9, CYP2C19 and CYP2D6. Results of extensive *in vitro* testing indicate little potential for pioglitazone to inhibit the metabolism of other drugs via these mechanisms. Since pioglitazone is not exclusively metabolised by any CYP isoform, it is unlikely that other drugs will interfere with its metabolism and vice versa. Metformin is not metabolized in all species.

Radioactivity was excreted rapidly in all species following administration of [^{14}C]pioglitazone, generally by the faecal excretion route and by the urinary excretion route in monkeys. In rats, pioglitazone-derived radioactivity was re-absorbed following excretion into bile. Metformin is primarily eliminated by renal secretion.

In conclusion, the preclinical pharmacokinetics and metabolism data supports the clinical pharmacokinetic experience with this drug in combination use with metformin.

Toxicology

- Single dose toxicity

Pioglitazone was well tolerated in both rats and mice after single oral doses up to 2000 mg/kg. LD50 values following intraperitoneal dosing were 181 mg/kg for mice of both sexes and 558 and 587 mg/kg for male and female rats, respectively. Oral metformin LD50 values were high enough in relation to a human dose intended in the clinical practice.

- Repeat dose toxicity

Repeated dose toxicity of pioglitazone after oral administration was studied in mouse (up to 13 weeks), rat (up to 13 weeks) dog (up to3 months) and monkey (up to 90 days). The NOAEL, defined as the highest doses that did not produce increased heart weight, were 3.2 mg/kg/day (mice), 1 mg/kg/day (rats), 1.1 and 3.4 mg/kg/day (male and female dogs, respectively), and 35.6 mg/kg/day (monkeys). Plasma volume expansion, because of the enhancement of the natriuretic properties of insulin, produced hemodilution (decreased erythrocyte count, haemoglobin and haematocrit) consistently observed through species at high doses. Cardiac hypertrophy was observed in rats and dogs, because of plasma volume expansion, were shown to be adaptive and reversible. There were also changes in the size and location of fat tissue in rodents at high doses, which were considered originated by an exaggeration of this pharmacological activity. Liver issues observed in rodents were not associated with elevation of liver enzymes or any signs of pathology, and were considered an adaptive response. The elevation of ALT values observed in dogs was reversible and not associated with histopathological changes. No evidence of toxicity was reported in chronic toxicity studies by oral and parenteral routes in rats, rabbits, and dogs.
There is a paucity of information on metformin, but information gained from studies in rats and rabbits dosed at greater than 100 mg/kg/day showed no abnormalities in growth, haematology, urea nitrogen or histopathology.

- Genotoxicity

Pioglitazone, along with several of its metabolites and impurities have been shown to have no genotoxic potential in a series of *in vitro* and *in vivo* studies
No evidence of genotoxicity of metformin was found in Ames test (S. typhimurium), mammalian gene mutation assay in mouse lymphoma cells, chromosomal aberration test in human lymphocytes, or in a mouse bone marrow micronucleus test.

- Carcinogenicity

There is no evidence of direct genotoxicity, mitogenesis or cytotoxicity with pioglitazone. There was no indication of any carcinogenic potential for pioglitazone in mice. However, there was a dose-related trend towards increased incidence of urinary bladder tumours in male rats at 4 mg/kg/day and higher, as mentioned in section 5.3 of the SPC. At the time of marketing authorisation for pioglitazone, the hypothesis presented by the applicant of bladder tumours associated with increased pH levels and subsequent calculi formation specific to male rats was considered reasonable. Since then, more PPAR agonists have come to clinical development and presented with similar hyperplastic and tumour responses. Therefore it may be considered that carcinogenicity and PPAR activation may be a class effect, but its transferability to man is as yet unknown. Following consultation between the CHMP and the applicant, the applicant has initiated a series of studies aimed at further investigating the mechanism by which pioglitazone results in a slight increase in urinary bladder tumours in male rats (see table of the risk management plan).

Long-term carcinogenicity studies with metformin have been performed in rats (≤900 mg/kg/day for 104 weeks) and in mice (≤1500 mg/kg/day for 91 weeks). No evidence of carcinogenicity was found in male or female mice or in male rats. In female rats, there was an increased incidence of benign stromal uterine polyps at the highest dose. A literature search was conducted on the terms metformin and cancer to note whether there is any possibility that metformin may promote tumour development in any way. The results suggest that the drug has a beneficial effect in cancer, and therefore it does not appear likely that metformin use in combination with pioglitazone increases any potential cancer risk.

- Reproduction Toxicity

Adverse birth and developmental effects are reported in the offspring of animals treated with pioglitazone (as mentioned in the SPC, section 5.3). These are often associated with adverse maternal effects, many of which have been attributed to the pharmacological action of the drug and which occur within the clinical dose/exposure range. It is suggested that the adverse effects of pioglitazone on the pups result from disturbances in maternal physiology rather than a direct toxic effect.
The fertility of male and female rats was unaffected by metformin administration at doses as high as 600 mg/kg/day. Metformin was not teratogenic in rats and rabbits at daily doses up to 600 mg/kg/day. In a recent report, embryotoxicity was observed in vitro in a mouse embryo model at the highest concentration of 100 µg/mL but not at 25 and 5 µg/mL, the latter concentration being similar to a maximum clinical serum level. Therefore, the FDC of pioglitazone/metformin should not be used during pregnancy; this is reflected in the wording of the SPC in section 4.6.

- Other toxicity studies

There were no manifestations of toxicity in the pigmented tissues of dogs or monkeys in studies of up to one-year duration.

Ecotoxicity/environmental risk assessment

The physico-chemical properties of pioglitazone and metformin and the predicted concentrations likely to enter the environment are not considered to represent a risk to the environment

4. Clinical aspects

Introduction

This application was submitted under Part B of the Annex to regulation 2309/93 as a full "mixed" application. The application is for a fixed dose combination product, Competact, containing two authorized ingredients, pioglitazone (as hydrochloride) and metformin hydrochloride. Actos (pioglitazone hydrochloride) was originally authorized in the European Union in October 2000 and is currently authorised for use as monotherapy or as combination therapy with either metformin or a sulphonylurea in patients with type 2 diabetes mellitus. Metformin was originally granted national authorisations in the EU from 1959 to 1997. Following a referral to the CPMP under Article 11 of Council Directive 75/319, as amended, a decision on a harmonised SPC for metformin was issued in February 2001.

The approved indication is for "the treatment of type 2 diabetes mellitus patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone." The claimed posology for this fixed dose combination product was for two strengths, 15mg/500mg and 15mg/850mg of pioglitazone (as hydrochloride) and metformin hydrochloride, respectively. The posology approved is for 15mg/850mg of pioglitazone and metformin hydrochloride.

The data relating to pioglitazone was original data that fulfilled all of the requirements for pharmacological tests and clinical trials and covers all of the indents in Part I.5 of Annex I Directive 2001/83/EC as amended. The clinical documentation concerning metformin was derived from bibliographic references. The applicant had conducted a detailed literature search to source suitable

publications for a review of the information. All aspects of metformin pharmacokinetics were assessed in published bibliographic reviews and study reports that together provided an extensive body of data.

The Applicant has performed 4 bioequivalence studies (2 of them relevant for this dossier) and one food- effect study. No clinical efficacy studies were conducted with the pioglitazone/metformin fixed-dose combination product. Clinical efficacy of the fixed-dose combination product is based on results of concomitant administration of the two drugs, clinical trials with the individual components and literature data for metformin. Coadministration studies of pioglitazone with metformin encompassed two short-term studies with 16 to 24 weeks' duration and a 104-week active-controlled long-term study.

A paediatric development programme for this medicinal product was not proposed and this was thought to be acceptable, given the fact that the indication is primarily for a condition of adults. No scientific advice has been given in relation to this application.

GCP

The Clinical trials involving pioglitazone and the biopharmaceutic studies with the fixed dose combination were conducted in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out under acceptable ethical standards of the Declaration of Helsinki and in accordance with the relevant GCP standards

Pharmacokinetics

- Absorption and Bioequivalence

Pioglitazone is rapidly absorbed reaching maximum plasma concentrations at 0.5-3hrs after drug intake. The absolute bioavailability ranged between 70% and 96% with a mean value of 83%. Food does not significantly influence the absorption of pioglitazone.
Metformin has an absolute oral bioavailability of 40-60% and peak concentrations are reached in approximately 2.5 hours. Absorption is incomplete with 20-30% of an oral dose recovered in the faeces. Absorption which is largely from the upper small intestine appears to be saturable resulting in less that dose proportional pharmacokinetics. Steady state plasma concentrations are reached within 24 hours at therapeutic doses and are usually in the range of 1-2 mcg/ml. Food decreases the extent of absorption by 25-40% and delays t_{max} by less than an hour.

In order to provide support for marketing approval of the fixed-dose combination product, the Applicant has performed 4 bioequivalence studies (2 of them relevant for this dossier) and one food-effect study:

The Applicant performed two bioequivalence studies (OPIMET-004 and OPIMET-005) to evaluate two new formulations, a bilayer formulation (Competact BL) and a micronised formulation (Competact MP), to demonstrate that pioglitazone 15 mg/metformin 500 mg (Competact MP and Competact BL) and pioglitazone 15 mg/metformin 850 mg (Competact MP and Competact BL) were bioequivalent to concomitant use of the separate commercial pioglitazone15 mg and metformin 500 mg or metformin 850 mg tablets, respectively. Upon completion of these studies, the Competact MP formulation was identified as suitable for commercial development. A fifth study (OPIMET-006) was performed to investigate the effect of food on the pharmacokinetics of pioglitazone, metformin and the fixed-dose combination. The commercial tablets used in these studies were Pioglitazone and Metformin. The bioequivalence studies and the food-effect study were designed in accordance with the relevant CHMP Notes for Guidance (EMEA CPMP/EWP/QWP/1401/98, 2001) and the relevant FDA guidance for industry (FDA, 2002).

Study OPIMET-004 was a single-centre, open-label, randomized, 3-period crossover study. Subjects were randomized to 1 of 6 treatment sequences in which they received a single oral dose of each

treatment: 15/500 mg pioglitazone/metformin fixed-dose combination micronised (MP) tablet, 15/500 mg pioglitazone/metformin fixed-dose combination bilayer (BL) tablet, and a 15 mg pioglitazone commercial tablet coadministered with a 500 mg metformin commercial tablet. The 3 treatment periods were separated by a washout period of 7 days. During each period, blood samples were collected at specified times up to 72 hours post treatment for the measurement of pioglitazone and metformin concentrations. Adverse events (AEs) and concomitant medications were monitored and recorded throughout the study. Other safety evaluations included clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examinations.
A total of 66 subjects (mean age of 31.3 years), including 29 male subjects and 37 female subjects, were enrolled in the study; 62 (93.9 %) subjects, including 28 males and 34 female subjects, completed the study. Four subjects discontinued the study early: 1 subject withdrew voluntarily; 1 subject withdrew because of an AE (mild allergic reaction); 1 subject withdrew because the subject became pregnant; and 1 subject was withdrawn because of a protocol violation.
Based on the primary analysis of AUC and C_{max}, exposure to pioglitazone and metformin following administration of the fixed-dose combination MP tablet was similar to that observed following coadministration of the separate commercial pioglitazone and metformin tablets. For both pioglitazone and metformin, the 90% CIs of the LS mean ratios of AUC(0-tlqc), AUC(0-inf), and Cmax were within the 80% to 125% range for bioequivalence (97.7 %, 102.5 %, and 95.0 %, for Pioglitazone, and 102.6 %, 102,8 %, and 99.0 % for Metformin, respectively). In addition, there were no statistically significant differences observed in treatment comparisons of T_{max} and λz for pioglitazone or metformin, and there were no notable differences between the treatments with respect to T1/2 or CL/F. The overall results thus demonstrate that the fixed-dose combination tablet (pioglitazone 15mg/metformin 500mg) is bioequivalent with respect to rate and extent of exposure compared to the separate components available commercially. This tablet strength, however, had been not pursued further during evaluation of the dossier.

Study OPIMET-005 had the same design as Study OPIMET-004 (see above) except that it compared 15/850 mg pioglitazone/metformin fixed-dose combination tablets with the 15 mg pioglitazone commercial tablet co-administered together with an 850 mg metformin commercial tablet.

A total of 64 subjects (mean age of 32.0 years), including 35 male subjects and 29 female subjects, were randomly assigned to treatment in the study at 1 study site, and 60 (93.8 %) subjects, including 33 male and 27 female subjects, completed the study. Four subjects discontinued the study early: 2 subjects withdrew voluntarily; 1 subject was withdrawn because the subject became pregnant; and 1 subject was lost to follow-up.
Based on the primary analysis of AUC and C_{max}, exposure to pioglitazone and metformin following administration of the fixed-dose combination MP tablet was similar to that observed following coadministration of the separate commercial pioglitazone and metformin tablets. As in Study 01-01-TL-OPIMET-005, for both pioglitazone and metformin, the 90% CIs of the LS mean ratios of AUC(0-tlqc), AUC(0-inf), and C_{max} were all within the 80% to 125% range for bioequivalence. Similar results were obtained even when carryover effects were included in the ANOVA model. With regard to the BL tablet, exposure to pioglitazone and metformin was also similar to that observed following coadministration of the separate pioglitazone and metformin commercial tablets. As with the MP tablet, the 90% CIs of the LS mean ratios for AUC(0-tlqc), AUC(0-inf), and C_{max} for both pioglitazone and metformin were within the 80% to 125% bioequivalence range, even when carryover effect was included in the ANOVA model. In addition, there were no statistically significant differences observed in treatment comparisons of T_{max} and λz for pioglitazone or metformin, and there were no significant differences between the treatments with respect to T1/2 or CL/F.

The overall results of the 2 studies OPIMET-004 and –005 demonstrate that the fixed-dose combination tablets (pioglitazone 15mg/metformin 500mg and pioglitazone 15mg/metformin 850mg) were bioequivalent with respect to rate and extent of exposure compared to the separate components available commercially.

Study OPIMET-006 was conducted to determine the effect of food on the exposure to pioglitazone and metformin after administration of the pioglitazone/metformin fixed-dose combination tablet. Both the Competact BL and MP formulations were investigated during this study, and the higher dose (pioglitazone 15 mg/metformin 850 mg) of each formulation was evaluated. The study was designed

so that all 28 subjects would receive both formulations with and without food, according to a randomly assigned sequence. After each dose, blood samples were collected at specified time points up to 72 hours post treatment for the measurement of pioglitazone and metformin concentrations. Administration of the 4 treatments was separated by a 7-day washout period.
An analysis of variance (ANOVA) with fixed effects for sequence, period, and treatment and random effect for subject nested within sequence was performed on time to maximum concentration (T_{max}), terminal rate constant (λz), and the natural logarithms of AUC(0-tlqc), AUC(0-inf), and C_{max} for pioglitazone and metformin. All 28 subjects were included in the pharmacokinetic and statistical analyses of the MP formulation. Based on AUC and C_{max} values, there was an absence of food-effect response on total and peak exposure of pioglitazone and on the total exposure of metformin. For pioglitazone, the 90% CIs of the LS mean ratios of AUC(0-tlqc), AUC(0-inf), and C_{max} were within the 80%, 125% range. For metformin, the 90% CIs of the LS mean ratios for AUC(0-tlqc) and AUC(0-inf) were within the 80%, 125% range, although there was a 13% decrease in total exposure to metformin based on the point estimate value. There was a food-effect response on the peak exposure of metformin. The 90% CI of the LS mean ratio for C_{max} was (65.4%, 79.1%), and the decrease in peak exposure to metformin was 28%. Drug dosing with food resulted in prolongation of T_{max} from approximately 1.6 to 3.5 hours for pioglitazone and from approximately 2.4 to 3.2 hours for metformin; both findings are consistent with what is known to occur for Pioglitazone and Metformin.
With respect to study OPIMET-006, a food- effect for metformin was shown (decreased C_{max} and AUC and delayed T_{max}). This influence of food on the pharmacokinetics of metformin was expected and it is also described when it is administered alone. The magnitude of this food-effect in the Competact tablet was lower than that described in the harmonised SPC for metformin. Overall, results from Study OPIMET-006 indicated that the food-effect responses for Competact MP were generally consistent with those previously reported for marketed Pioglitazone and Metformin.

- Distribution, Elimination, and Dose proportionality

Single and multiple dose studies with *Pioglitazone* demonstrate linearity of pharmacokinetics in the therapeutic dose range. The volume of distribution is small with a mean of 0.253L/kg. Pioglitazone is extensively bound to plasma proteins. Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. The clearance is sensitive to changes in both the intrinsic capacity of the liver to oxidise drugs and the free fraction in plasma and was found to be independent of dose in the range of 2-60mg. Regular monitoring of liver function is therefore recommended in the SPC (section 4.4), and liver impairment constitutes a contraindication (section 4.3 of the SPC). The terminal elimination half-life following intravenous administration was found to vary between 3.5–9.0 hrs with a mean value of 5.8 hrs. Following oral administration, the terminal half-life observed in most studies is in the same range. Renal elimination of unchanged pioglitazone is negligible.
Metformin reached steady state plasma concentrations within 24 hours at therapeutic doses and are usually in the range of 1-2 mcg/ml. It is rapidly distributed and does not bind to plasma proteins. No metabolites or conjugates have been identified. As metformin is primarily excreted unchanged in the urine, significant accumulation may occur in renal impairment, resulting in increased risk of lactic acidosis. Therefore, Competact is contraindicated in patients with moderate renal impairment, with a creatinine clearance< 60ml/min, as indicated in the SPC, section 4.3. In addition, it is recommended in the SPC's section 4.4 to measure renal function regularly.

- Special populations and Pharmacokinetic interaction studies

Pioglitazone: The profile of metabolites in diabetic patients is similar to that seen in healthy volunteers. Kinetics is not appreciably different in the elderly. Drug interaction studies indicate that pioglitazone does not inhibit the metabolism of drugs cleared by the P450 system. Pioglitazone did not affect the steady state pharmacokinetics of sulphonylureas. Metformin has no major effect on serum pioglitazone concentrations.

Metformin doses of 0.5 to 1.5g have an absolute oral bioavailability of 40 to 60%. The discrepancy between the amount of drug absorbed and the amount available may result from presystemic clearance or binding to the intestinal wall. There was no statistically significant difference in pharmacokinetics of metformin between healthy subjects and patients with T2DM shown in clinical studies.
Potential interactions between metformin and acarbose, guar gum and cimetidine exist

Pharmacodynamics

No new pharmacodynamic studies were submitted for this FDC application.

- Mechanism of action and Primary and Secondary pharmacology

Pioglitazone is a thiazolidinedione and a potent and highly selective agonist for the nuclear receptor peroxisome proliferator-activated receptor (PPAR)γ. PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ receptors modulates the transcription of a number of insulin-responsive genes involved in the control of glucose and lipid metabolism. This results in an enhancement of insulin sensitivity, which manifests in reduced hepatic glucose production, increased glucose uptake in muscle, and reduced lipolysis in adipocytes. Data in humans to support this mechanism have been done using the euglycaemic clamp technique and intravenous glucose tolerance tests with application of a minimal model. Studies investigating the pharmacodynamics of pioglitazone in diabetic subjects have shown that once-daily administration of pioglitazone at doses of 15, 30 or 60mg improved both FBG and postprandial blood glucose levels, the hypoglycaemic effect being maintained throughout the day. This effect appeared within 2 weeks of treatment. The fact that both fasting and postprandial blood glucose profiles are improved by pioglitazone suggests that pioglitazone may improve glucose metabolism in diabetic patients. Significant reductions in postprandial insulin were seen in these studies but almost no reductions in fasting insulin were seen. This suggests that pioglitazone has no direct stimulatory effect on the beta cells of the pancreas.

The glucose lowering effect of metformin results from a 25-30% decrease in the rate of endogenous glucose production. This results in a similar relative reduction in fasting plasma glucose levels. It was also shown that metformin reduces glucose production either by decreasing gluconeogenesis or by decreasing glycogenolysis. To a lesser extent, plasma glucose levels are decreased by the stimulation of peripheral glucose uptake by skeletal muscle and adipose tissue, which is more likely secondary to the reversal of glucotoxicity and not a direct pharmacological effect. Unlike sulfonylureas, metformin does not stimulate insulin secretion.

In addition metformin decreases plasma free fatty acid concentration by 10-30% in individuals with diabetes. Elevated levels of free fatty acid may contribute to increased hepatic glucose production and peripheral insulin resistance. By ameliorating the effects of high free fatty acid (lipotoxicity) on pancreatic β cells, metformin may also partially correct the impaired insulin secretion that characterizes the type 2 diabetic state. Metformin was found in high concentrations in the small intestine and may also decrease intestinal glucose absorption. Metformin decreases fasting plasma glucose by 2.5-3.5 mmol/L with a 1-2 % decline in haemoglobin A_{1c} (HbA_{1c}).

When used together, pioglitazone and metformin provide additive benefits and lead to improved control of blood glucose levels. Since neither pioglitazone nor metformin stimulate insulin secretion from the pancreatic beta-cells, the benefits are realised without commensurate increases in circulating insulin levels.

Clinical efficacy

No clinical studies have been conducted with Competact. Demonstration of efficacy of this FDC relies on the clinical studies for Actos as monotherapy and in combination therapy with metformin (which have been previously submitted and evaluated as part of the Actos application) and on bibliographic data for the metformin component. The support for the fixed-dose combination pioglitazone/metformin product relies largely on 1 pioglitazone plus metformin combination therapy study submitted in 1999 (PNFP-027), and 2 pioglitazone plus metformin combination therapy studies submitted between 2002 and 2004 (EC410 and PNFP-342).

- Dose response studies

A number of placebo-controlled studies with pioglitazone as monotherapy have been performed and submitted as part of the 1999 MAA. From these data, a dose-response relationship was found from 15

to 45 mg, the magnitude of the glycaemic response in the range of 0.5% to 2.0% for HbA_{1c} and 1 to 4 mmol/L (20-70 mg/dL) for blood glucose.
Metformin immediate-release tablets can be administered twice daily with meals if <2000 mg is needed for blood glucose control or three times daily in divided doses with meals for daily dosages >2000 mg. In clinical trials, metformin monotherapy reduced FPG by 52-92 mg/dl and HbA_{1c} by 1.4-2.0% versus placebo over the dose range of 1700 mg-3000 mg daily (Garber, 1997; Stratton, 2000; De Fronzo, 1995). The majority of these trials enrolled overweight or obese patients with type 2 diabetes in whom glycaemic control was inadequate with diet and exercise alone. Reductions in these glycaemic parameters are log-linear and dose-dependent over the dose range of 500-2000 mg daily (Garber, 1997).
Dose-response effects thus have been demonstrated for both actives.

- Main studies

The studies which are considered pivotal to support the combination use of pioglitazone and metformin are studies EC410, PNFP-342 and PNFP-027. The design of these studies is summarised in Table 1

Table 1 Overview of Pioglitazone Plus Metformin Combination Therapy Studies

Study	Duration	Treatments (a)	Patients (ITT)	Critical Design Features
EC410	104 weeks	Pioglitazone 15-45mg + Metformin	310	Dose-titration (tolerability based) Change from baseline analysis
		Gliclazide 80-320mg + Metformin	310	
PNFP-342	24 weeks	Pioglitazone 30mg + Metformin	411	Fixed dose
		Pioglitazone 45mg + Metformin	416	
PNFP-027	16 weeks	Placebo + Metformin	160	Fixed dose
		Pioglitazone 30mg + Metformin	168	

(a) In EC410 the comparator drugs were titrated to maximal tolerated dose.

These studies differed in duration of treatment, use of control, and inclusion of a dose-titration period. They were similar in that pioglitazone treatment was added to an existing metformin regimen that provided insufficient glycaemic control. Also, the dosage of metformin could not be changed once the double-blind treatment period had started, so that all patients were maintained on a stable, maximal tolerated dose of metformin throughout the treatment period. The combination therapy studies shown in table 1 included 1305 pioglitazone-treated patients. The subsequent sections summarize the 3 studies, with an emphasis on study EC 410.

METHODS

Study Participants
In Study EC410, Pioglitazone vs. Gliclazide as Add-on to Metformin was tested in patients with type 2 diabetes, 35 to 75 years of age, with HbA_{1c} 7.5% to 11.0% and fasting C-peptide greater than or equal to 1.5ng/mL who were currently being treated with metformin at 50% or greater maximum recommended dose or at the maximum tolerated the dose for at least 3 months were included into this double-blind, randomised, active-comparator study.

In study PNFP-342, 30 mg Pioglitazone vs. 45 mg Pioglitazone as Add-on to Metformin was tested in patients whose type 2 diabetes was poorly controlled by their current metformin therapy (HbA_{1c} ≥8% at screening) and who had a BMI 25 to 45 kg/m2. After a 1-week single-blind placebo lead-in period, subjects received 24 weeks of double-blind treatment during which their dosage of metformin could not be adjusted. In study PNFP-027, 30 mg Pioglitazone was compared vs. Placebo as Add-on to Metformin in male and female patients 30 to 75 years of age with BMI between 25 and 45, HbA_{1c} greater than or equal to 8.0%, and C-peptide greater than 1 ng/mL who had received constant treatment with metformin for at least 30 days prior to participation in the study for treatment of type 2 diabetes.

Table 2 summarizes the entry criteria of all 3 studies:

Table 2 Summary of Entry Criteria

	EC410	PNFP-342	PNFP-027
Age (yr)	35-75	>18	30-75
Period on existing antidiabetic medication	≥3 months	≥30 days	≥30 days
Previous antidiabetic medication prohibited	Insulin, any sulphonylurea, any TZD	Insulin, any TZD	Insulin, any TZD
BMI (kg/m^2)	-	25-45	25-45
HbA_{1c} (%)	7.5-11.0	≥8	≥8
Fasting C-peptide (ng/mL)	≥1.5	-	>1

TZD = thiazolidinedione.

Treatments, Objectives
In Study EC410, eligible patients were randomly assigned to receive pioglitazone or gliclazide for 104 weeks in addition to their existing metformin therapy. Patients were initially seen every 4 weeks during a forced titration period of 16 weeks where the dose of study drug was increased at each visit from 15 mg od to 45 mg od pioglitazone or 80 mg od through 4 steps to 160 mg bid gliclazide. The dose of study drug was increased at each time point during titration unless the patient had not tolerated the previous dose or the investigator considered that the patient was at risk of experiencing hypoglycaemia, or other tolerability issues, should the dose of study drug be further increased. In such circumstances, a reduction in dose by one titration step was permitted. Thereafter, dose of study drug was maintained throughout the remaining 88 weeks of the study.
In study PNFP-342, after a 1-week single-blind placebo lead-in period, subjects received 24 weeks of double-blind treatment during which their dosage of metformin could not be adjusted. In study PNFP-027, each individual patient's dose of metformin remained constant throughout the duration of the study, and any other antidiabetic medications were discontinued at study entry. Patients were randomly assigned to treatment with either 30 mg pioglitazone or placebo in addition to metformin for a period of 16 weeks.

Outcomes, Endpoints
For all 3 studies the primary efficacy measure was the change in HbA_{1c} from baseline to last value, with a number of secondary endpoints in each study.

Statistical methods
In Study EC410, the data presented for all efficacy variables analyses the change from baseline to Week 104 (LOCF) using an ANCOVA model with the factor treatment and the baseline value as covariate testing the null hypothesis that there is no treatment difference (2-sided test, α=0.05). In addition, 95% confidence intervals were calculated.

RESULTS

Participant flow
Withdrawal rates with pioglitazone after 2 years were not higher than those in shorter-term studies. Although the studies were performed in different geographical locations, this suggests that pioglitazone and metformin combinations were generally effective and well tolerated over the longer term. The most common reasons for withdrawal were adverse event or lack of clinical efficacy but these were not more common than with gliclazide in study EC410.

In Study EC410, 74% of patients in the pioglitazone group completed 2 years of treatment compared with 76% in the gliclazide group. Adverse events and lack of efficacy accounted for approximately half of the withdrawals with no major difference between the groups.

Baseline data
In Study EC410, 630 patients who were randomly assigned to treatment (317 patients to pioglitazone and 313 patients to metformin) were included. The mean age of the patients was approximately 56 years. Approximately 50% of the population was male and more than 99% was Caucasian. Mean BMI was 32.6. Mean HbA_{1c} at baseline was slightly higher in the pioglitazone plus metformin group (8.7%) than in the gliclazide plus metformin group (8.5%). There were no other significant differences among the treatment groups for any of the baseline variables. The mean dose of study drug at the end of dose titration was 38.9 mg pioglitazone and 211.7 mg gliclazide.
Table 3 gives an overview of the baseline characteristics of all 3 studies.

Table 3 Summary of Demographics and Baseline Characteristics

	EC410 N=630	**PNFP-342 N=827**	**PNFP-027 N=328**
Gender (%M/%F)	50/50	58/42	57/43
Mean age (yr)	56	54	56
Race (%)			
Caucasian	99.7	64.8	83.8
Black	0	19.0	7.3
Hispanic	0	13.5	7.0
Other	0.3	2.7	1.9
Median Duration of Diabetes (yr)	4.3	-	-
Mean BMI (kg/m^2)	32.6	32.4	32.1
HbA_{1c} (% P/C) (a)	8.71/8.53	9.92/9.86	9.75/9.86
FPG (mmol/L) (a)	11.8/11.3	13.1/13.0	14.3/14.0

(a) HbA_{1c} and FPG are displayed for individual treatment groups: pioglitazone/gliclazide (EC410); 30 mg/45 mg (PNFP-342); pioglitazone/placebo (PNFP-027).

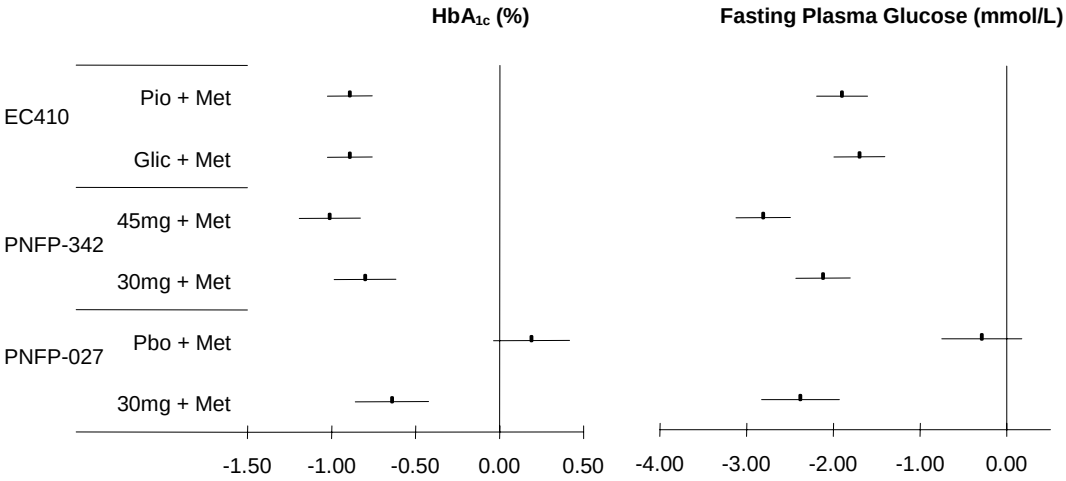
In general, demographics and baseline characteristics were well matched across the studies. Whilst most patients in study EC410 were Caucasian, more non-Caucasian patients whereas in studies PNFP-342/PNFP-027 (35% and 16%, respectively). Patients in the US studies PNFP-342/PNFP-027 had higher HbA_{1c} and FPG compared to EC410. Within study EC410, baseline glycaemic variables were slightly higher in the pioglitazone group than the gliclazide group (Table3).

In EC410, patients received the maximally tolerated dose of study drug. The mean doses at the end of dose titration were 38.9 mg pioglitazone and 211.7 mg gliclazide.

In study EC410, eligible patients had to be receiving companion medication (SU or metformin) at greater than equal to 50% of the maximum recommended dose or at their maximum tolerated dose. Only 4% of patients were on less than 50% the maximum recommended dose of concomitant metformin. No such criteria were set in PNFP-342 and PNFP-027; however, the mean percentage of maximum recommended daily dosage of metformin was 61% in both PNFP-342 and PNFP-027, with similar percentages in the individual treatment groups within each study.

Outcomes and estimation
For all 3 studies the primary efficacy measure was the change in HbA_{1c} from baseline to last value. These data are presented in Figure 7 and show that doses of 30 mg and 45 mg pioglitazone are effective in improving glycaemia when concomitantly administered with metformin. The data also suggest that peak effect may not be seen until 6 months treatment as in PNFP-342 and that these effects are maintained to 2 years as observed in EC410.

Figure 1 Glycaemic Control with pioglitazone in combination therapy: Change from Baseline to Endpoint ± 95% CI for HbA_{1c} (%) and Fasting Plasma Glucose (mmol/ L)



In all studies, glycaemic control was further improved following addition of pioglitazone to metformin therapy, at doses up to 45 mg daily. PNFP-027 was a short placebo-controlled study, which showed the benefit of adding 30 mg pioglitazone with a decrease from baseline in HbA_{1c} at 16 weeks of 0.64% compared with an increase in placebo of 0.19%. In study PNFP-342, both 30 mg and 45 mg showed significant decreases from baseline in HbA_{1c} of 0.80% and 1.01%, respectively, after 24 weeks treatment. This level of improvement was similarly found in study EC410, which compared the addition of pioglitazone with that of gliclazide and continued treatment for 2 years, at which time the decrease from baseline was maintained with pioglitazone at 0.89% but had showed signs of deterioration from maximal effect under gliclazide with a change from baseline at 2 years of 0.77%. Decreases in fasting plasma glucose ranged from 1.8 to 2.8 mmol/L in pioglitazone groups and were found to be statistically significantly greater than those observed with placebo after 16 weeks (2.12 mmol/L) and gliclazide after 2 years (1.1 mmol/L).

Glycaemic responder rates are summarised in Table 4 below and responders were defined as the following:

EC410: Reduction in HbA_{1c} of greater than 0.6%.

PNFP-342 & PNFP-027: A HbA_{1c} responder was any patient whose HbA_{1c} reduced to less than or equal to 6.1% or decreased from baseline by greater than or equal to 0.6%.

Table 4 HbA_{1c} and FPG Responder Rates to pioglitazone as combination therapy with existing SU/metformin treatment

	EC410 (a)		PNFP-342 (b)		PNFP-027 (b)	
	Pio+Met	**Glic+Met**	**30mg+Met**	**45mg+Met**	**Pbo+Met**	**30mg+Met**
HbA_{1c} responder rate (%)	61.1	57.1	55.8	63.3	21.6	54.0

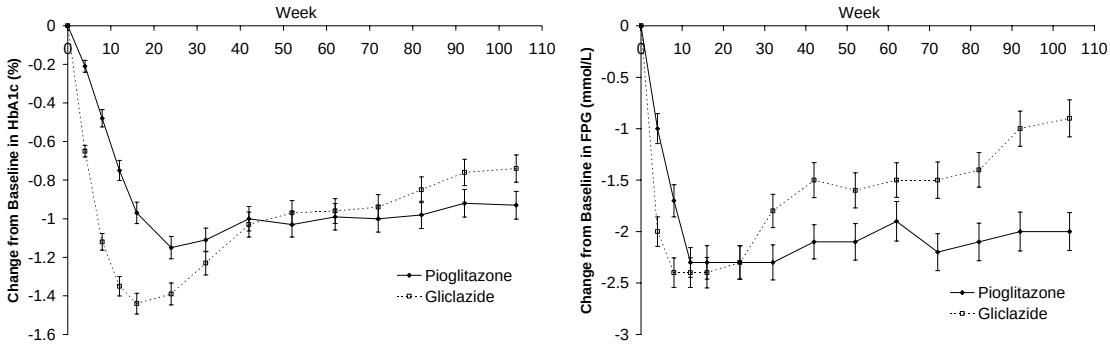
(a) HbA_{1c} responders were classified as patients with a decrease from baseline of >0.6%.
(b) HbA_{1c} ≤6.1% or HbA_{1c} decreased from baseline by ≥0.6%.
Pio=pioglitazone, Met=metformin, Glic=gliclazide, 30 mg=30 mg pioglitazone, 45 mg=45 mg pioglitazone, Pbo=placebo.

Responder rates demonstrate that pioglitazone, as combination therapy with metformin, effectively improved glycaemic control in approximately 60% of patients and that the proportion of patients that respond to therapy is comparable to that seen with the commonly used combination of metformin and sulphonylurea.

In Study EC410, the time courses of HbA_{1c} and FPG in Figure 1 demonstrate that after the initial improvements, glycaemic control was better sustained with pioglitazone as add-on to metformin than by gliclazide, where despite the rapid initial effect, deterioration in control was apparent from Week 16 onwards. In the gliclazide group, there was an increase in mean HbA_{1c} of 0.70% from the nadir at Week 16 to Week 104. In contrast, the onset of effect was slower with pioglitazone with the nadir at

Week 24, but improvements were much better maintained thereafter with an increase in HbA_{1c} of only 0.22% from this point until Week 104.

Figure 2 Study EC410: Pioglitazone and Gliclazide as Add-On to Metformin: Change from Baseline ± SEM in HbA_{1c} [%] and FPG (mmol/L) – LOCF – ITT Population



After 2 years treatment on top of metformin, decreases from baseline in HbA_{1c} were 0.89% with pioglitazone and 0.77% with gliclazide. This represents a difference of 0.12% (-0.31, 0.07) between the groups. The reduction in HbA_{1c} was reflected in the number of responders, with almost one third of patients in each treatment group achieving final HbA_{1c} less than 7.0%.

Analysis of changes in FPG revealed a greater decrease from baseline with pioglitazone than with gliclazide ($P<0.001$ between groups). Furthermore, analysis of the per-protocol (PP) population included only those patients who received at least 72 weeks treatment with study drug, and in these patients, the difference between groups in HbA_{1c} change from baseline at Week 104 was statistically significant (-1.07% and -0.76% for pioglitazone and gliclazide respectively; $P=0.003$). Taken as a whole, these data strongly suggest that in the long term, pioglitazone offers better sustainability of glycaemic control then gliclazide as an adjunct to metformin. This was further supported in the current study by the coefficient of failure, which was lower with pioglitazone than with gliclazide (0.20%/yr and 0.44%/yr respectively; $P<0.001$).

- Discussion on clinical efficacy

No clinical efficacy studies were conducted with the pioglitazone/metformin fixed-dose combination product. Clinical efficacy of the fixed-dose combination product is based on results of concomitant administration of the two drugs, clinical trials with the individual components and literature data for metformin. Coadministration studies of pioglitazone with metformin encompassed two short-term studies with 16 to 24 weeks' duration and a 104-week active-controlled long-term study. In all three studies, glycaemic control was improved following addition of pioglitazone to existing metformin therapy.

Pioglitazone at doses of 30mg (PNFP-027 and PNFP-342) and 45mg (PNFP-342) and up to 45mg (EC410) in combination with metformin also improved insulinaemia, insulin processing, as well as the abnormalities associated with diabetic dyslipidaemia, namely elevated triglycerides, low HDL-cholesterol, and a preponderance of small dense LDL particles.

There are no specific dose titration studies to determine the optimum pioglitazone dose to be combined with metformin. Doses lower than 30 mg, of pioglitazone (e g 15 mg), as approved in the pioglitazone SPC, have not been studied in combination with metformin, they have only been tested in combination with SU. This is taken into consideration in the posology section of the SPC, where a dose of 30 mg pioglitazone (together with 1700 mg metformin) per day, taken as two tablets, is recommended.

Pioglitazone has been dosed in all these studies once a day in accordance with the currently recommended posology section of the pioglitazone SPC. However, the FDC tablet is to be taken in two divided doses due to the need to divide the metformin dose. To address this concern, the applicant provided during the evaluation evidence that pioglitazone 30 mg bid and 60 mg od results in a similar

overall exposure, and supplementary data from small studies with pioglitazone given in divided doses. Thus, the CHMP accepted the interchangeable efficacy of a pioglitazone dose when given divided in two doses instead of the same dose once a day, for this application.

Clinical safety

Safety information on pioglitazone and metformin fixed dose combination therapy is derived from 3 studies in which pioglitazone and metformin were co-administered (EC410, PNFP-0342, and PNFP-027). These studies have been previously submitted and assessed by the CHMP.

- Patient exposure

The clinical programme for this pioglitazone variation comprises 3 completed controlled clinical studies. A total of 1,785 patients were enrolled in these studies. Of this total, 1,312 received pioglitazone as combination therapy with metformin. The remaining patients received metformin plus a comparator agent (either gliclazide or placebo). More than 70% of pioglitazone patients included in EC410 completed 2 years of treatment. The characteristics are shown in Table 1 (section efficacy).

The duration of treatment ranged from 16 to 104 weeks in the combination therapy studies. Dosing regimen for pioglitazone was 30 or 45 mg once daily (od), with the exception of the first portion of EC410, which had a forced dose-titration period during which subjects could initiate treatment at 15 mg od.

As would be expected in a type 2 diabetic population, there were high incidences of vascular disorders (mainly hypertension), other metabolic and nutritional disorders, cardiac disorders, and eye disorders. As is usual in a relatively elderly population, musculoskeletal disorders (mainly arthritis) were also commonly noted as concomitant diseases.

There was a slight imbalance between pioglitazone and gliclazide patients in the incidence of cardiac disorders (mainly angina) in EC410 (pioglitazone 19.2%, gliclazide 13.4%) and vascular disorders (pioglitazone 68.1%, gliclazide 62.6%). The use of concomitant medication reflected the reported concomitant diseases.

- Adverse events

The data show that the number of patients with at least 1 AE, withdrawing because of AEs, with an SAE, or dying in the course of the studies were similar in pioglitazone-treated groups and comparator groups.

Table 5 Incidence of Most Common Adverse Events (≥3% of Patients in Any Treatment Group) – Combination Therapy Studies

	EC410		PNFP-342		PNFP-027	
Preferred Term	Pio + Met N=317	Glic + Met N=313	30 mg + Met N=411	45 mg + Met N=416	Pbo + Met N=160	30 mg + Met N=168
Hypoglycaemia NOS	2.2%	11.5%	2.7%	4.3%	0.6%	0.6%
Hypertension NOS	1.6%	1.9%	1.0%	1.2%	1.3%	1.8%
Arthralgia	2.8%	6.1%	3.6%	4.3%	1.3%	3.6%
Headache	4.7%	4.2%	4.6%	5.3%	1.9%	6.0%
Nasopharyngitis	4.1%	4.8%	1.5%	1.7%	2.5%	3.0%
Diarrhoea NOS	1.6%	4.2%	5.8%	4.8%	6.3%	4.8%
Back pain	4.4%	7.3%	2.4%	4.8%	3.1%	4.2%
Oedema peripheral (a)	6.6%	0.6%	2.9%	11.3%	2.5%	4.2%
Upper respiratory tract infection NOS	5.0%	6.4%	12.4%	13.5%	15.6%	15.5%
Influenza	5.0%	3.2%	1.7%	2.9%	3.8%	2.4%
Cough	2.5%	4.2%	2.4%	3.6%	3.1%	3.6%
Dizziness	2.8%	1.6%	5.4%	4.8%	0.6%	0.6%
Nausea	2.8%	2.2%	5.8%	3.6%	3.8%	1.8%
Bronchitis NOS	2.5%	4.2%	1.9%	3.1%	1.9%	1.8%
Weight increased	3.5%	2.2%	2.9%	6.7%	0.6%	1.8%

Consistent across the 3 studies, pioglitazone was associated with higher reporting of oedema. The terms oedema not otherwise specified, aggravated oedema, and oedema peripheral were grouped in EC410, and the incidence of the grouped term was 6.3% and 2.2% for pioglitazone and gliclazide, respectively.

Weight increase was reported as an AE for pioglitazone when added to metformin in 3.5% of patients compared to 2.2% with gliclazide in EC410. No other AEs for pioglitazone and metformin combination showed any consistent excess over gliclazide and metformin combination. The incidence of weight gain was slightly lowered when pioglitazone 30 mg was added to metformin in study PNFP-027 compared to EC410 1.8% vs. 2.2% respectively); this may be a result of the shorter treatment duration in study PNFP-027. A slightly higher incidence rate for weight gain was noted in the pioglitazone plus metformin group in PNFP-342 compared to either pioglitazone 30 mg plus metformin groups in studies EC410 and PNFP-027. The highest rates were noted for the pioglitazone 45 mg plus metformin group in PNFP-342 (6.7%). However, no subject in the pioglitazone 45 mg plus metformin group discontinued study drug dosing because of weight gain.

When pioglitazone was added to a standard treatment with metformin, there was an increased incidence of peripheral oedema, weight gain, arthralgia and headache as compared to placebo plus metformin.

- Serious adverse events and deaths

No deaths were reported in the PNFP-342 or PNFP-027 combination therapy studies. In the 2-year study EC410, 2 patients (0.6%) in each treatment group died during the study. The causes of deaths were in the main cardiovascular or cerebrovascular in aetiology, as might be expected in a diabetic population. There was no death of unusual or unexpected aetiology suggestive of any toxic effects of pioglitazone.

In PNFP-027, when pioglitazone was added to metformin, there were higher rate of SAEs (4.2%) than when placebo was added to metformin (1.3%). However, it should be noted that patient numbers for these latter 2 groups were rather low at about 160 patients per group, and therefore point estimates of rates were liable to large variation. Similar reporting rates of SAEs were observed with the addition of

both 30 mg pioglitazone (4.4%) and 45 mg pioglitazone (3.8%) to metformin in the 24-week study, PNFP-342.
In the 2-year EC410 study, overall SAE reporting rates for pioglitazone and gliclazide when added to metformin were similar (11.4% with pioglitazone vs. 11.2% with gliclazide). The incidence of cardiac events was higher for pioglitazone in EC410 than for gliclazide when either drug was added to metformin.

- Laboratory findings

Placebo-controlled studies showed that during treatment with pioglitazone there were small decreases in haemoglobin and haematocrit compared to placebo. The decreases were in the order of about 4% relative to baseline values. This is mentioned in the SPC section 4.4. Whilst similar changes were seen with pioglitazone in EC410, gliclazide also showed decreases in haemoglobin, haematocrit, and red blood cells albeit slightly less than those observed with pioglitazone.

Similarly to that seen during the MAA, study results submitted in the 2002 and 2004 safety summaries showed no evidence of an increased risk of hepatotoxicity with pioglitazone relative to comparator agents. These data show that effects observed at 1 year are sustained to 2 years and still evident. Analyses of changes in individual patients showed no excess in changes of liver enzymes to >3 ULN with pioglitazone compared with comparator treatments.

- Physical findings related to safety

Controlled trials have shown weight increases with pioglitazone treatment. The greatest increase in weight was seen in insulin combination trials and the least with metformin combination therapy. A study investigating effects of pioglitazone on body composition had demonstrated that weight gain mainly could be explained by increases in subcutaneous fat. Pioglitazone also seemed to induce a redistribution of intra-abdominal fat to the subcutaneous fat compartment.

Table 6 Mean ± SD Changes in Weight from Baseline to End of Treatment

	EC410		PNFP-342 (a)		PNFP-027 (a)	
	Pio + Met N=314	Glic + Met N=311	30 mg + Met N=278	45 mg + Met N=281	Pbo + Met N=160	30 mg + Met N=167
Baseline (kg)	92 ± 16	93 ± 17	95 ± 18	95 ± 18	94 ± 18	92 ± 16
Change at Endpoint (kg) (b)	2.2 ± 5.32	1.1 ± 4.54	1.0 ± 0.25	2.3±0.23	-1.4 ± 2.7	1.1 ± 3.4
Minimum (c)	-16.4	-32.4	DU		DU	
Maximum (c)	22.0	21.5	DU		DU	

After 2 years, in EC410, weight had further increased in pioglitazone groups, but the rate of weight gain was slower during a second year of treatment. At the end of 2 years, pioglitazone-treated patients had mean gained 2.3 kg in comparison to 1.1 kg with gliclazide. This represents a mean weight gain over 2 years of less than 5% with pioglitazone treatment. Some patients had still lost weight with pioglitazone as shown by the range of weight changes and the median values.

- Adverse events by organ system or syndrome

<u>Cardiovascular</u>

In the 2-year study, which used gliclazide as a comparator, the incidence of cardiac events was generally lower when gliclazide was added to metformin than with pioglitazone (1.8% vs. 3.8% for SAEs, respectively, and 3.8% vs. 7.9% for AEs, respectively. Upon inspection of individual events, the main difference appeared to be a lower incidence of angina with gliclazide. In this study, there was a higher proportion of patients with cardiac and vascular conditions at baseline in the pioglitazone group. Reporting rates for episodes of heart failure in the placebo and active comparator controlled trials showed no excess in pioglitazone groups compared to non-pioglitazone groups.

Oedema

Oedema occurs with pioglitazone treatment in 6% to 8% of patients treated over a 1-year period. In by far the majority of AE reports, such oedema was reported as mild or moderate and only very rarely caused withdrawal of treatment with pioglitazone. Only one patient withdrew for oedema in EC410. Although reporting of oedema occurred more frequently during the first few months of treatment, it was also reported later during treatment. With continued treatment, in some cases oedema resolved. Oedema was not associated with development of heart failure.

Anaemia

Although pioglitazone treatment is known to be associated with small decreases in mean haemoglobin and haemotocrit, the reporting rates of anaemia as an AE were similar with pioglitazone and active comparator treatments. In the course of long-term (2 years) treatment with pioglitazone, anaemia in as an AE was reported for 1.6% of patients treated with pioglitazone and 0.6% of patients treated with gliclazide; 1 pioglitazone treated patient discontinued study drug dosing because of anaemia. The clinical trial results do not suggest that pioglitazone is associated with large decreases in haemoglobin and haematocrit. Furthermore, there is no evidence from AE data from the trials of any toxic effect of pioglitazone on bone marrow.

- Discontinuation due to adverse events

The rate of AEs causing discontinuation from the study are shown in the table below for those preferred terms that occurred in at least 3% of patients in any treatment group.

Table 7 Most Common (≥3%) Adverse Events Causing Discontinuation of Study Drug

	EC410		PNFP-342		PNFP-027	
	Pio + Met N=317	Glic + Met N=313	30 mg + Met N=411	45 mg + Met N=416	Pbo + Met N=160	30 mg + Met N=168
Hyperglycaemia NOS	0.6%	0.3%	2.7%	1.7%	2.5%	1.8%
Hypoglycaemia NOS	0.0%	1.0%	2.7%	4.3%	0.6%	0.6%
Nausea	0.0%	0.0%	0.2%	0.7%	3.8%	1.8%
Headache	0.3%	0.0%	0.2%	0.5%	1.9%	6.0%
Oedema peripheral	0.6%	0.0%	0.5%	1.0%	2.5%	4.2%

The proportion of patients discontinuing for any individual AEs was low and the rate of discontinuations did not increase over time in the 2-year study. Hyperglycaemia was the most common AE leading to discontinuation among pioglitazone-treated patients across these studies, with oedema peripheral occurring at the same rate as hyperglycaemia in studies EC410 and PNFP-027. Hypoglycaemia was most common amongst gliclazide patients. Weight gain and oedema rarely caused discontinuation with pioglitazone in the short-term combination therapy studies, and only 1 patient in the long-term EC410 study discontinued because of oedema (oedema peripheral).

Vital signs, physical findings, and other observations related to safety

For all studies, administration of the pioglitazone/metformin fixed-dose combination tablets resulted in very minor changes in vital sign parameters, and these minor changes were similar to those noted following the coadministration of the individual commercial tablets.

Three subjects (OPIMET-004) had physical examination findings at Post treatment/Early Termination that were not present at Baseline or Screening. These findings were reported as adverse events of pharyngolaryngeal pain, oropharyngeal swelling, hypersensitivity, face oedema, and pruritus.

For all studies, a standard 12-lead ECG was recorded for each subject at the Screening and Post treatment/Early Termination Visits. All 12-lead ECG recordings were interpreted by a qualified physician as normal or abnormal. Clinical significance was assessed for all abnormal recordings. For all studies, few subjects had 12-lead ECG recordings interpreted as abnormal and none were considered clinically significant or associated with an adverse event.

No unexpected AE, laboratory abnormalities, changes in vital signs and physical finding were seen during bioequivalence trials (studies OPIMET-004, -005 and –006). As expected, gastrointestinal AEs were the main tolerability limitation, although these AEs were mild and do not lead to treatment discontinuation. The limited provided data do not suggest a different tolerability of the fixed-dose formulation to be marketed as compared to commercial tablets given separately.

- Post marketing experience

It is estimated that since the first launch in the US in July 1999 until 31 July 2004 pioglitazone has been cumulatively prescribed to a total of 4,677,000 patients in the U.S., 637,000 patients in Japan since introduction of the product in December 1999 and 330,000 patients in Europe since introduction of the product in November 2000.

A summary of the post-marketing data as presented in the ISS in 2002 and then the cumulatively reported events up to 31 July 2004 as presented in the 6th to 10th PSUR have been provided. In addition to routine safety surveillance performed within the company, a pharmacovigilance plan including a number of special studies and investigations to confirm the safety of pioglitazone is in place (see section Risk Management Plan). Overall, the safety profile of pioglitazone as judged by ADR reporting from an estimated 3 million or so patients from the market up to Feb 2002 plus 2 million or further from then up to 31 July 2004 were reassuring and confirmed the safety profile as seen in clinical trials. No unexpected toxicity of pioglitazone was identified during postmarketing experience in these reports.

Recently, 35 cases of macular oedema have been noted in post marketing reports in patients treated with pioglitazone. The information provided by these reports is limited although many cases appear to be associated with peripheral oedema. Most of the reports are from the United States in patients with more advanced disease. Concomitant insulin was used in 14 of 29 of these cases with no information in 6 cases. Pre-existing eye disease was noted in 18 cases with macular oedema in 6 cases, diabetic retinopathy in another 4 cases and no eye disease in one case. It is unclear whether or not there is a direct association between pioglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity and appropriate ophthalmologic referral should be considered. This is reflected in the SPC (sections 4.4 and 4.8) and the Package Leaflet (sections 2 and 4). This information is in line with the identical information introduced into the SPC and PL for Actos via a type II variation adopted 1.6.2006.

On the market, about 30% of pioglitazone therapy is in free combination with Metformin, and only about 30% are as monotherapy. From the spontaneous reports from the market and as observed in the clinical trials with combination therapy as outlined in detail in this ISS, there appears to be no major difference in the ADR profile. The only emerging difference seen is the increase of reports of heart failure, when pioglitazone is given in combination with insulin, and the increase of reports of hypoglycaemia when pioglitazone is given in combination with sulfonylureas. The combination with Metformin however, does not yield a shift in ADR profile in the reports from the market.

- Discussion on clinical safety

The use of Pioglitazone in combination with Metformin for the treatment of type 2 diabetes mellitus was granted with the first marketing authorisation application for pioglitazone, based on the results of one placebo-controlled clinical trial (PNPF–027). Later on, two additional combination therapy clinical trials were performed (Studies PNPF-342 and EC410), confirming previous results and conclusions and providing information on longer-term use of pioglitazone with metformin. A total of 1,785 patients were enrolled in these studies. Of these, 1,312 received pioglitazone as combination therapy with metformin. When pioglitazone was added to an established regimen with metformin given at the maximum tolerated doses, only those specific AEs related to pioglitazone therapy such as oedema and weight gain were reported in a higher rate in this group of patients than in patients treated with other comparators added to metformin based regimen (e.g.. glicazide, placebo). The incidence of oedema in these studies ranged from 2.9% to 11.3% across studies, which was within the expected range. Weight increase was seen in up to 3.5% of patients treated with pioglitazone+metformin as compared to 2.2% in patients treated with glicazide+metformin.

The safety profile of pioglitazone and metformin in combination was the sum of the AE profiles of each product given as monotherapy, with gastrointestinal disorders, weight gain and oedema being the most commonly reported. Neither unexpected AEs nor worsening of the individual AE profiles were seen in any of the clinical trials performed with this combination.

Since the MAA in EU, in November 2002, PSURs have not identified any concern related to a possible interaction leading to a worsening of the safety profile of these products when given in combination, which is relevant considering that up to 30% of pioglitazone use is in combination.

In addition to the above described safety profile of the combination of both active principles, data from the proposed fixed-dose tablet have been provided (studies OPIMET-004, -005, and –006). The limited available data in healthy volunteers do not suggest a different tolerability of the fixed-dose formulation as compared to commercial tablets given separately. There are no data of administration of this FD tablet to diabetic patients. Although diabetics may suffer from specific gastrointestinal disturbances, it is not expected to result in different tolerability of the new FDC tablet as compared to the old tablets.

Remaining concerns regarding long-term safety and lack of outcome data with thiazolidinediones in general were not addressed by this data.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan

Summary of the Risk Management Plan

Safety concern	Proposed pharmacovigilance activities	Proposed / established risk minimisation activities
Hepatic dysfunction	1. Routine pharmacovigilance including review in PSURs 2. Annual review and report on Hepato-biliary events 3. Results from completed hepatic safety study in pioglitazone 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 including review in PSURs 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
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
Lactic acidosis	1. Routine pharmacovigilance including review in PSURs 2. Review of ADR reports to assess compliance with SPC recommendations 3. Trend analysis on frequency of reporting	Contraindication in section 4.3 of the SPC Precautions and recommendations for pre-disposing risk factors, and early presenting features in section 4.4 of the SPC

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology

The pharmacology of pioglitazone and metformin has been investigated for each drug separately. No preclinical studies of the combination were conducted, which was found to be acceptable by the CHMP. Overall the general pharmacology studies corroborate the information previously available for the individual components and support the combined use.
From the pharmacokinetic point of view, the rat was the most relevant species for non-clinical efficacy and safety studies. In male rats, pioglitazone caused, as a well-known effect, an elevation of the rate of bladder tumours. The relevance of this finding is unknown, and this information has been included in the SPC.

Efficacy

The efficacy of Competact taken as a tablet of 15 mg pioglitazone and 850 mg metformin twice daily was sufficiently demonstrated. In the absence of clinical efficacy studies conducted with the pioglitazone/metformin fixed-dose combination product, this has been demonstrated by bioequivalence studies and bridging data from clinical trials with the individual components.
The tablet strength and posology approved corresponds to 30 mg pioglitazone and 1700 mg metformin per day, respectively. A second tablet strength of 15 mg pioglitazone and 500 mg metformin was retracted by the applicant in April 2006, thus resolving concerns by the CHMP that the resulting daily dose of 1000 mg metformin per day may result in underdosing of this component. The single tablet strength available does not allow for dose titration, which is reflected in the SPC.

Safety

The safety profile of pioglitazone and metformin in combination was the sum of the adverse event profiles of each product given as monotherapy, with gastrointestinal disorders, weight gain and oedema being the most commonly reported. Neither unexpected AEs nor worsening of the individual AE profiles were seen in any of the clinical trials performed with this combination. Except for reports of macular oedema, no change in the safety profile was derived from the post marketing experience with pioglitazone either, where usage is in part as a combination with metformin. From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the SPC. Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The applicant committed to perform readability testing of the English Patient Information Leaflet and to report back within two months of marketing authorisation.

Risk-benefit assessment

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- no additional risk minimisation activities were required beyond those included in the product information.

The fixed dose combination of pioglitazone and metformin was considered justified by the CHMP having the benefit of simplification of therapy thus enhancing compliance with treatment. Taking into account that efficacy has been shown sufficiently for the strength of 15 mg pioglitazone and 850 mg metformin taken twice daily, the benefit/risk ratio was considered positive by the CHMP, provided that patients are titrated with pioglitazone to the recommended dose of 30mg daily before being switched to Competact.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Competact in the treatment of type 2 diabetes mellitus patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone, was favourable and therefore recommended the granting of the marketing authorisation.