SCIENTIFIC DISCUSSION

1. Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease characterised by hyperglycaemia, due to inadequate control of levels of blood glucose by the pancreatic hormone insulin and/or abnormal resistance to insulin. The principle aim of diabetes treatment is to control blood glucose levels, in order to prevent mortality and long-term complications, including retinopathy, renal dysfunction, neuropathy and non-traumatic limb amputations. Initial treatment includes modifications to diet and exercise, followed by prescription of an oral antidiabetic agent. However, during the first 3 years of monotherapy with a first-line oral antidiabetic medication, up to 50% of patients treated with a sulphonylurea (SU) exhibit inadequate glycaemic control. Upon failure of monotherapy, combination therapy is initiated, typically with a second (and sometimes third) oral antidiabetic agent, with or without insulin. Combination therapy may enhance tolerability, simplifies the treatment regimen and may prevent treatment failures that might result from missed doses. With the implementation of more stringent targets for A1C levels (<6.5%), the use of a second oral antidiabetic agent is likely to increase, occur earlier in the treatment course, or both. As the importance of combination use is increasingly recognised, FDCs have been developed with the gold standard, metformine (MET). These include a FDC with glyburide and MET, and a FDC with rosiglitazone (RSG) and MET. However in subjects for whom MET is inappropriate because of contraindication or intolerance, these FDC treatments are not an option. The rationale to develop a new FDC is that in subjects contraindicated to, or intolerant of MET, who are no longer achieving glycaemic control on SU monotherapy, the only oral combination option is the concomitant addition of a thiazolidinedione (TZD). Compliance with treatment is an important factor in order to achieve the target glycaemic control. The combination of two different classes of antihyperglycaemic agents in a single tablet can simplify the treatment and may help to ensure compliance although this is largely speculative. When considering combination therapy for the treatment of T2DM, it is beneficial to select agents with complementary mechanisms of action in order to provide additive therapeutic benefits without exacerbating treatment-limiting side effects. Various European SPCs include approval for co-prescribing SU, MET and TZD. TZDs, such as pioglitazone (PIOG) or RSG, are oral glucose-lowering drugs specifically designed for T2DM. They reduce insulin resistance in peripheral tissues such as adipose tissue and skeletal muscle, and the liver through the activation of peroxisome proliferator-activated receptor-gamma (PPARγ). SUs such as glimepiride (GLIM) stimulate insulin production in the pancreas and increase insulin sensitivity at the cellular level. As shown in the Table 1, the available SUs have variable potency and durations of action.

Table. 1 General Characteristics of SUs

Generic name	Dose range (mg/d) & (duration of action, h)	General characteristics
First generation		
Tolbutamide	500-3000 (6-10)	Shortest acting with fewest side effects; no longer available commercially
Chloropropamide	250-500 (24-72)	Rapidly absorbed; may have extra-pancreatic effects; causes most serious side effects, including prolonged hypoglycaemia and severe hyponatraemia; given once daily or in divided dose.
Tolazamide	100-750 (16-24)	Effects persist despite a gradual decline in the insulin secretory response, suggesting some extra-pancreatic effects; 5 times more potent than tolbutamide, equally potent to chloropropamide on a milligram basis; once daily dosing.
Second generation		
Glipizide	2.5-20* [5-20 for XL] (16-24) *upper dose can be 40 mg in US	Binds extensively to plasma proteins; metabolism via CYP system; once daily dosing.
Glibenclamide (glyburide)	2.5-20 (18-24)	Long-acting, binds to plasma proteins through non-ionic bonds; binds tightly to the 140 kDa protein at the SUR of the pancreatic beta cell membrane; given once daily; given in single or divided doses.
Gliclazide	40-320 (12)	Intermediate-acting; binds to plasma proteins; stimulates the secretion of insulin in the fasting as well as postprandial states; enhances insulin secretion over time, and continues

		to reduce the production of endogenous glucose after several months of treatment; given once or twice daily.
Glimepiride	0.5-8 (~24)	Long-acting; highly protein bound; given once daily; acts primarily on the membrane receptors on pancreatic beta cells, but also is internalised into pancreatic beta cells, where it acts on insulin secretory granules.

SUR=SU receptor.
(a) GLIM is referred to as either a second- or third-generation SU.

On a milligram for milligram basis, second- and third-generation SUs are 20 to 50 times more potent and have more prolonged biological action than first-generation agent. Second- and third-generation SUs also penetrate into cell membranes faster than their older counterparts because they have greater lipid solubility and more selective binding capacity. Second-generation SUs include glibenclamide, gliclazide, and glipizide. GLIM is sometimes described as a third-generation SU. Potency varies among the second- and third-generation SUs. Glibenclamide is approximately 2 times more potent than glipizide on a milligram per milligram basis. GLIM is about 2 times as potent as glibenclamide in stimulating glycogenesis and lipogenesis on a molar basis in in-vitro studies. T2DM involves deficient insulin activity due to a decrease in circulating insulin concentration (insulin deficiency) and a decrease in the response of peripheral tissues to insulin (insulin resistance). The combination of the individual active substances from these two classes, as proposed, is not inappropriate, especially since both constituent drugs substances are taken once daily with or without food. Of the approved antidiabetic combination therapies, concomitant use of PIOG with a SU is among the most frequently used in clinical practice. Once-daily administration could be seen to offer the benefits of combination treatment in a single tablet, and thereby potentially improve patient compliance and glycaemic management.

This Marketing Authorisation is for a fixed dose combination product (FDC), PIOG/GLIM, containing two previously authorized ingredients, PIOG hydrochloride and GLIM in two strengths: 30mg/4mg and 45mg/4mg tablets (initially for three strengths including also 30mg/2mg but this strength was withdrawn from the application by MAH). Tandemact is indicated for the treatment of patients with type 2 diabetes mellitus who show intolerance to metformin or for whom metformin is contraindicated and who are already treated with a combination of pioglitazone and glimepiride. Pioglitazone hydrochloride, a TZD, was originally authorized in the European Union in October 2000 and is currently authorized for use as monotherapy or as combination therapy with either MET or SUs in patients with T2DM. PIOG is a potent and selective PPARγ agonist. Activation of PPARγ nuclear receptors modulates the transcription of insulin-responsive genes involved in the control of carbohydrate and lipid metabolism. As a result of these actions, PIOG reduces insulin resistance in the peripheral tissue and in the liver, thereby increasing insulin-dependent glucose disposal and decreasing hepatic glucose output. GLIM is a second-generation SU originally authorised via the mutual recognition procedure in 1995. It is indicated to treat hyperglycaemia in patients with T2DM either as first-line monotherapy or as an add-on to MET or insulin. GLIM lowers glucose levels primarily by stimulating release of insulin from pancreatic β cells. As with other insulin secretagogues, GLIM binds to and blocks the ATP-dependent potassium channels on the surface of pancreatic β cells, thereby leading to membrane depolarisation, increased calcium uptake, and insulin release. PIOG/GLIM is indicated in the treatment of patients with T2DM who are already treated with a combination of PIOG and SU or whose diabetes is insufficiently controlled with SU monotherapy.

This application was submitted under Part B of the Annex to Regulation 2309/93 and is a full "mixed" application in accordance with Article 8(3) and Annex I Part II.7 of Directive 2001/83/EC as amended. The data relating to PIOG was original data that fulfils 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 data previously assessed for the Community authorisations for PIOG were not resubmitted in this application. A bibliographic review to describe the clinical profile of GLIM and SU class has been submitted for this application.

2. Quality aspects

Introduction
The product is a fixed combination containing PIOG (as hydrochloride) and GLIM as active substances. Three strengths were initially proposed containing 30 mg /2mg, 30 mg/4mg or 45 mg /4 mg of PIOG (as hydrochloride) /glimeperide but the lowest strength was withdrawn from the application by MAH. They were presented as tablets. Apart from this difference in strength, the formulations are identical, the excipients were povidone, cellulose microcrystalline, croscarmellose sodium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, and polysorbate 80. The tablets are supplied in HDPE bottles.

Active Substance

PIOG hydrochloride
This active substance has been authorised as a result of an earlier centralised procedure for the same applicant. 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. PIOG hydrochloride has a specific crystalline form and has not demonstrated polymorphism.PIOG 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. PIOG hydrochloride specifications includes tests for description, identification (IR, UV, HPLC and Chloride ion), assay 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 appropriate for controlling the quality of this active substance. The re-test period proposed is acceptable according to the stability data submitted.

GLIM
Information on GLIM has been supplied in the form of Active substance master file (ASMF). GLIM is a crystalline white powder. No asymmetric carbon atom is present and it is practically insoluble in water. Two crystalline polymorphic forms of GLIM are known and the applied manufacturing process yields the thermodynamically more stable form. The presence of this form is controlled routinely in thebatch analysis. The manufacturing and control information on GLIM was provided in the form of an ASMF and was evaluated as satisfactory. Adequate In-Process Controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents, have been presented. GLIM specifications are in accordance to the latest Ph Eur monograph including tests for appearance, solubility, identification, related substances, water content, sulphated ash, and impurities. , solubility, identification (IR, UV), polymorph identification (IR), heavy metals, related substances. The tests and limits in the specifications are considered appropriates for controlling the quality of this active substance. Batch analysis data of six production batches GLIM are provided. The results are reproducible and comply with the specifications. Stability results of GLIM stored in double polyethylene bags in HDPE containers at 25ºC/60%RH over 36 months for three batches have been submitted together with 24 months for another three batches (25ºC / 65%RH). The parameters tested were description, solubility, identification, loss on drying, related substances, cis- isomer and assay. No significant changes occurred in the parameters studied. 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 most important properties to influence the formulation was the low solubility in water of both PIOG and GLIM. Therefore, particle size of both active substances played an important factor in the drug formulation development. Excipients are used at unexceptional concentrations and have been show compatible with the active substances. However, to optimise the stability of each active, taking into account the individual (different) stability profiles, the matrix for each active substance was different. This was solved by having the actives and excipients separated in a bi-layered tablet design. The excipients used are povidone, cellulose microcrystalline, croscarmellose sodium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, and polysorbate 80. The excipients are conventional and meet the requirements in Ph. Eur. Lactose monohydrate is manufactured from bovine milk. The supplier confirms that the milk used in the manufacture of the lactose is sourced from healthy animals under the same conditions as for human consumption. The

primary packaging chosen was HDPE bottles. Details and specifications of the packaging components and identity tests for all components together with batch analytical data were provided. The container material has been certified as food grade.

- Manufacture of the Product

The active substances are granulated separately using Pharmacopoeial excipients and compressed into a bilayer tablet. The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process in one production-scale batch for the 45 mg/4 mg tablet strength and 50% of full scale batch for the 30 mg/ 4mg tablet strengths and is satisfactory. The in process controls are adequate for this tablet preparation. The batch analysis data show that the 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), related substances (HPLC), dissolution, (Ph Eur), uniformity of content (HPLC, Ph Eur), assay of the active 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 confirm satisfactory uniformity of the product at release.

- Stability of the Product

Three pilot batches (1/7.5 full scale) of each tablet strength in HDPE containers were placed on stability under ICH conditions. The batches were tested for appearance, loss on drying, hardness, assay, related substances, dissolution and microbial limits. They have were exposed to 25º C/60% RH for 18 months and 40º C / 75% RH for 6 months. Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were a number of minor unresolved quality issues without impact on the clinical efficacy or safety of the product, therefore the applicant made a commitment to resolve these as post-opinion follow-up measures

3. Non-clinical aspects

Introduction

The Application contained extensive documentation concerning non-clinical pharmacology, pharmacokinetics and toxicology of PIOG and GLIM. The non-clinical data relating to PIOG is derived from bibliographic references and original data of the Community authorisations for PIOG. The non-clinical documentation concerning GLIM is derived from bibliographic references and a justification for the use of the literature to replace the results of toxicological and pharmacological tests is provided. No new non-clinical studies were conducted with the fixed formulation compound. In view of the length and extent of clinical experience obtained with co-administration of commercially available PIOG and GLIM, CHMP considered that the omission of animal studies cited under indents 4.2.1 to 4.2.3 (a to f) inclusive of Annex 1 Directive 2001/83/EC was justified. In the case of carcinogenicity studies and genotoxicity studies no supportive studies or bibliographic references were provided. The company provided a CPMP opinion following an Article 10 referral for GLIM as supportive data for the justification of a lack of carcinogenicity and genotoxicity studies (3rd August 1998 CPMP/1416/98).

Pharmacology

- Primary pharmacodynamics

PIOG

PIOG is a PPAR gamma agonist with an EC_{50} of 470 nmol/l. It also has relatively weak PPAR alpha activity. Activation of PPAR gamma is dose dependent. Of the major metabolites, MIV has some contribution to the efficacy of PIOG in man. PIOG enantiomers occur spontaneously in both human and animal plasma and there is no obvious difference in absorption or elimination between them. PIOG, like other PPAR agonists' mechanism of action is not fully elucidated, but the reduction in insulin resistance involves modulation of intracellular signalling mediated via the nuclear PPARγ. PIOG reduces TNF-alpha (increased expression is associated with diabetes/obesity) and improves metabolic abnormalities in Wistar fatty rats. It increases insulin sensitivity in isolated soleus muscle and in isolated adipocytes without changing insulin binding (carried out ex-vivo on tissues from Wistar fatty rats). PIOG improved insulin mediated glucose metabolism in KK mice, and aged insulin resistant dogs also showed reduced fasting and postprandial plasma lipid and glucose levels. No effect is anticipated in IDDM and PIOG is unlikely to cause hypoglycaemia. The combination of PIOG and either SUs/ voglibose/MET was studied and effects on reducing plasma and urinary glucose were additive (noted in rats).

GLIM

GLIM is a long acting SU that stimulates the rapid secretion of insulin from beta- pancreatic cells. This action is mediated by binding to the SURx receptor a regulatory subunit of the ATP-sensitive potassium channel on the beta cell membrane, resulting in membrane depolarisation and subsequent calcium influx and insulin release. Irespective of the route of administration, GLIM has a more rapid onset of activity and longer duration of action than glibenclamide. The longer lasting effects of GLIM are attributed at least in part to the extra-pancreatic effects through the stimulation of increased insulin independent glucose utilisation by a number of other tissues (fat and muscle cells) via stimulation of glucose transporter isoform 4 (GLUT4) translocation and increased activities of the key metabolic enzymes glycerol-3-phosphate acyltransferase (GPAT) and glycogen synthetase and more recently though the proposed activation of the PPARγ receptor in adipocytes. Comparison to other SU indicates that GLIM had the greatest degree of extra-pancreatic activity, resulting in reduced potential to induce hypoglycaemic events and improved ability to lower blood glucose levels. Inukai *et al.* (2005) and Fuken *et al.*,(2005) have both demonstrated the ability of GLIM to directly bind to PPARg receptor in a competitive manner to known agonists (RSG) and active gene promoter containing PPAR-responsive element and alter mRNA levels of PPAR-g targeted genes including aP2, leptin and aiponectin. Furthermore, GLIM has demonstrated the ability to induce differentiation of adipocytes in a PPARγ dependent manner. The PPARg agonist activites differ between the two published papers and ranges between 16% and 20% of that of PIOG at 1μM. Despite interaction with the SUR2A receptor of the K_{ATP} channels on cardiac cells, GLIM displayed significantly less cardiovascular activity than other existing SUs and the least cardiotoxic potential. The free combination of PIOG and glibenclamide has been studied in Wistar fatty rats, a model of NIDDM, and demonstrated an improvement in glucose intolerance and a suppression of over insulin secretion. GLIM has been demonstrated to be superior to glibenclamide with respect to a reduction in plasma glucose and plasma insulin levels with reduced potential for cardiotoxicity. Based on this evidence the combination of GLIM and PIOG would be more beneficial with improved safety in comparison to the combination of PIOG and glibenclamide.

- Secondary pharmacodynamics

PIOG

The effects of PIOG on fat mobilisation (distribution) in animal models of NIDDM are explicable in terms of the drug's known pharmacology. The distribution of white and brown adipose tissue is modulated by PIOG. 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. Brown fat is increased by a direct action of the drug and this is thought to be important in sustaining normalisation of insulin sensitivity in obese hyperglycaemic states. 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 PIOG 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. A recent clinical study has shown that there is indeed an increase in body fat associated with PIOG treatment. However, this increase is restricted to subcutaneous fat and visceral fat is reduced. This is important because visceral fat is the main predictor of cardiovascular risk. In addition, weight increase in clinical studies is still associated with an improvement in metabolic outcome, specifically glucose

and lipids, leading to an improvement in calculated cardiovascular risk. Therefore the re-disposition of adipose tissue seen in animals is of no relevance to clinical outcome.

GLIM

SU have previously been related with increased mortality due to cardiovascular dysfunction. SU bind to and regulate SUR receptors on K_{ATP} channels not only on β–pancreatic cell membranes (SUR1) but also those of the K_{ATP} channels of myocardial cells (SUR2A). GLIM has a lower affinity for SUR2A and a lower level of activity on K_{ATP} channels at therapeutic concentrations in comparison to other SUs. GLIM has no effect on the electrical threshold, conduction time or refractory period in the isolated rabbit heart. In both rat and guinea pig isolated cardiac myocytes, the IC_{50} for inhibition of rilmakalim-activated K_{ATP} channels was higher for GLIM than glibenclamide. These receptors have a role in ischaemic preconditioning which is a cardioprotective mechanism. Glibenclamide abolished the cardioprotective effect conferred by ischemic preconditioning and diazoxide, in comparison to GLIM, which had no effect. Comparison of GLIM and glibenclamide *in vivo* demonstrated that endotoxin-shocked rats administered glibenclamide displayed elevated blood pressure. Following iv administration of GLIM or glibenclamide, glibenclamide produced signs of ischaemia (change in ST-interval of the ECG) in all rats whilst GLIM had almost no effect. In streptozotocin-diabetic rats, glibenclamide produced a lethal cardiogenic shock preceded by serious ECG changes in all animals. In GLIM-treated rats, effects were less pronounced and only 2 of the 11 animals died. In normal open-chest dogs the effects of GLIM on all parameters (reduced coronary blood flow, increased coronary resistance, depressed mechanical activity of the heart, enhanced myocardial O_2 extraction, reduced serum potassium levels and an induced moderate endocardial ST-segment elevation) were less than those provoked by glibenclamide. Subsequent studies in normal and alloxan-diabetic dogs further demonstrated that GLIM effects were weaker than glibenclamide on reductions in mean arterial blood flow, contractile force, rate of myocardial contraction and relaxation, and pressure. Posa *et al.,* (2002) highlighted the metabolic effects of SU in the heart of diabetic dogs. Both glibenclamide and GLIM reduced the rate of pyruvate extraction, however the rate of lactate extraction was not consistently affected by glibenclamide whereas GLIM reduced lactate extraction rates with a more moderate reduction in diabetic animals. Overall, action on the metabolic systems was weaker for GLIM than glibenclamide suggesting a lesser disturbance of the cardiovascular system in diabetes. Further positive effects on cardiac function were demonstrated by the ability of GLIM and glibenclamide to increase the chance of survival of life-threatening arrhythmias by reducing the incidence of irreversible ventricular fibrillation during myocardial ischemic-reperfusion. Investigation of the effects of glibenclamide and GLIM on myocardial infarction in coronary ligated rats revealed increased scar thinning and inhibition of thickening of the non-infracted ventricular septum by glibenclamide, in contrast GLIM did not precipitate scar thinning and inhibited the dilation of the left ventricular cavity. Unlike GLIM, glibenclamide appears to contribute to the deterioration of the heart function by promoting the shift from a compensated state to a decompensated state. Based on the *in vitro* studies GLIM appears to have improved cardiac safety profile over other SU due to a reduced binding of SUR2A regulator and reduced activity at cardiac K_{ATP} channel sat therapeutic concentrations. Based on the *in vivo* action of GLIM in dogs, GLIM appears to be safer with respect to cardiotoxicity than glibenclamide another SU.

- Safety pharmacology programme

PIOG

A series of general pharmacology studies were carried out on PIOG. For the *in vivo* experiments this was formulated in 0.5% methylcellulose or gum Arabic, *in vitro* 0.55% DMSO was used. There appears to be a strong placebo effect where 0.5% methylcellulose is used, this is not the case with gum arabic, the impact of this effect on the interpretation of the results is unclear. The probability of PIOG exerting clinically significant pharmacological action on any of the systems tested is low.

Central and Somatic Nervous System Effects:

An Irwin screen in mice (4 males/group) showed a decrease in spontaneous motor activity within 15 minutes of an oral dose of 300 mg/kg. The effect lasted 2 hours and there was no change in response to external stimulus. Skeletal muscle co-ordination in mice was unaffected at 300 mg/kg po in the inclined screen, traction and Rotarod tests. A dose of 30 mg/kg po did not prevent tonic extensor seizures in mice induced by a supra-maximal electric shock (15 mA, 600 V AC for 0.2 seconds). Doses of 100 or 300 mg/kg po produced a slight reduction in seizure but this was not significant compared to phenytoin 15 mg/kg po. There was no alteration in Phenobarbital induced sleeping time in mice at up to 300 mg/kg po. Doses of >100 mg/kg po reduced the frequency of writhing episodes following acetic acid (0.6%) 0.1 ml/10g ip, to a similar extent as aminopyrine 50 mg/kg po (i.e. about

50%). The fact that placebo also reduced writhing by 46% suggests that this is not a true 'analgesic' effect. Doses up to 300 mg/kg po had no effect on body temperature in rats. Electrodes were implanted in the dorsal hippocampus and basolateral amygdala of cats (2/sex). After 2 weeks recovery, recordings were made under conscious, unrestrained conditions before and for 7 hours after a dose of 30 mg/kg po. No effects on spontaneous EEG or behaviour were noted. No effect on the flexor reflex of the anterior tibial muscle in anaesthetised cats was seen at 10 mg/kg intra-duodenally.

Cardiovascular Effects
Haemodynamic studies were performed in conscious and unconscious male, Beagle dogs and in conscious rats via indwelling arterial catheters. An oral dose of 30 mg/kg had no effect on BP, heart rate or general behaviour during the 7 hour observation period in conscious dogs. Similarly, 300 mg/kg po had no affect on these parameters in the 5 hours post-dose in conscious rats. There was no alteration, compared to placebo, in BP, heart rate, renal blood flow or superior mesenteric blood flow, in unconscious dogs given 10 mg/kg intra-duodenally.

Autonomic Nervous System Effects
Intra-duodenal administration of 10 mg/kg to anaesthetised cats had no effect on the bradycardic response to stimulation of the right cervical vagus nerve, pressor response to bilateral carotid occlusion, contraction of the nictitating membrane caused by pre-ganglionic stimulation of the cervical sympathetic nerve or BP responses to nor-adrenaline, acetylcholine or histamine. Acetylcholine, histamine and barium induced contractions were unaffected by 10^{-5} M PIOG, but the dose-response curves were right shifted at 10^{-4} M.

Renal Effects
The effects of oral PIOG, 30, 100 and 300 mg/kg, were compared to hydrochlorothiazide, 10 mg/kg, in rats. There was a significant reduction in urinary volume and sodium, but not potassium, excretion at the top dose only with PIOG and an increase in urinary volume and sodium excretion with the hydrochlorothiazide. A reduced urinary volume was seen with placebo.

Gastrointestinal Effects
Oral doses of 0 (placebo), 30, 100 or 300 mg/kg PIOG inhibited gastric emptying in rats by 233, 29, 144, 240 % compared to control. The same doses reduced intestinal transport time from a control of 77.3 % of the intestinal length in 60 minutes to 63.0, 73.6, 73.6, and 51.3 % respectively. PIOG at 10^{-5} M had no effect on the spontaneous motility of the rabbit ileum in vitro; however10^{-4} M decreased the magnitude on the contractions immediately, reaching a maximum of 95% at 20 minutes.

GLIM
No non-clinical safety pharmacology studies with GLIM have been reported in the literature. In view of the extensive clinical experience with GLIM since authorisation in 1996, the lack of published data in animals is considered justified.

- Pharmacodynamic drug interactions

PIOG
No specific studies of potential drug interactions were carried out. The Expert Report contains a discussion of several relevant studies in the pharmacodynamic and pharmacokinetic sections of the dossier. The weight of evidence suggests that serious adverse drug interactions with insulin, glibenclamide or voglibose are unlikely.

GLIM
No reports of non-clinical studies have been found. In the opinion of CHMP it is acceptable.

Pharmacokinetics

PIOG is a high permeability and low solubility drug; GLIM is a low solubility drug. Good absorption was observed in animals and in humans for both drugs with low hepatic first-pass effect for PIOG. Plasma protein binding of PIOG and GLIM across species was relatively high. Radioactivity was widely distributed to tissues in rats after [^{14}C]PIOG and [^{14}C]GLIM administration, and was excreted into milk of lactating rats. PIOG and GLIM are extensively metabolized in all species including humans. PIOG did not induce cytochrome P450 in rats. All 6 human Phase I metabolites of PIOG were identified in mice, rats, dogs, and monkeys. PIOG is metabolized primarily by CYP2C8 and CYP3A4 but the contribution of these CYP

isoforms to the metabolism of PIOG 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 PIOG to inhibit the metabolism of other drugs via these mechanisms. Radioactivity was excreted rapidly in all species following administration of [^{14}C] PIOG, generally by the faecal excretion route and by the urinary excretion route in monkeys. GLIM was excreted rapidly following administration of [^{14}C] labeled material principally via the urine in rabbit and man and the faeces in mouse, rat, dog, and monkey. In rats, both PIOG-and GLIM-derived radioactivity was reabsorbed following excretion into bile. Based on the pre-clinical pharmacokinetic and metabolism data there is no evidence to support the possible interference on individual pharmacokinetic parameters if the active substances are administered via FDC. Therefore the summarized data herein supports the combination use of PIOG and GLIM.

Toxicology

- Single dose toxicity

In single dose studies, the oral LD_{50} for PIOG was greater than 2000 mg/kg in both rats and mice. The acute toxicity of GLIM after oral or intraperitoneal administration was very low in Wistar rats with all animals surviving the maximal administrable doses of 10,000 mg/kg and 5950 mg/kg, respectively and displayed no signs of toxicity. Based on acute toxicity studies there is a wide safety margin for effects based on oral LD_{50} values for both PIOG and GLIM.

- Repeat dose toxicity (with toxicokinetics)

In repeat dose toxicity studies (between one and twelve months duration) in 4 species (rats, mice, dogs, monkeys), the adverse effects of PIOG appeared to be caused as a result of metabolism (increased fatty deposits, anaemia, cardiac hypertrophy). As this effect was noted in multiple species, it may be of clinical concern. The effects were caused by exaggerated pharmacological activity, rather than a toxicological consequence. No treatment-related toxicologically relevant effects were observed in either rats or dogs, administered GLIM, with the exception of a slight reduction in bodyweight in 2 dogs dosed at 320 mg/kg/day. Bilateral subcapsular cataracts were observed in 1 males and 1 female, the relevance of which is unclear. Consistent with the pharmacological action of the compound, decreases in serum glucose levels were observed which was non-dose related and this was accompanied with degranulation of pancreatic β-cells. These changes were completely reversible.

- Genotoxicity

Neither PIOG nor MET are considered to have genotoxic potential.

- Carcinogenicity

Bladder tumours have been noted in male rats after long-term PIOG administration (in 2 year carcinogenicity studies). The carcinogenic potential of PPAR agonists in general is of significant concern to regulators. Both PIOG and GLIM display PPARγ agonist activity. Due to the high protein binding of both PIOG (>98%) and GLIM (>99% in all species tested and >99.5% in humans) the applicant committed to evaluate the potential of the individual compounds to influence the individual free fractions and in the presence of such an interaction between PIOG and GLIM on the protein binding profile, to recalculate of the safety margins in relation to carcinogenic potential for both GLIM and PIOG based on plasma concentrations (AUCs) of the free fraction in relation to the proposed dosage regimens. The solution for these concerns was proposed to be handled as part of the follow up measures. GLIM has been shown to cause uterine adenocarcinomas in rats at doses of (345 mg/kg). Safety factors based on systemic exposure of females rats and humans were considered high enough to exclude a risk to patients. In mice there was an increased incidence of islet cell hyperplasia and of the islet cell adenomas; these are regarded as resulting from the chronic stimulation of the beta cells.

- Reproduction Toxicity

Adverse birth and developmental effects have been noted in the offspring of animals treated with PIOG. This effect was considered as a result of the physiological disturbances that occurred in the mother, rather than as a result of direct toxic effect on the foetus. Administration to the rat revealed no effects on fertility, course of pregnancy or delivery. Malformations (e.g. eye malformations, fissures and bone anomalies) occurred in rats and rabbits, and in rabbits the number of abortions and intrauterine deaths were increased. Sulphonylurea-derivatives like GLIM pass into the breast milk.

Ecotoxicity/environmental risk assessment

The use of this compound is not considered to represent a significant risk to the environment.

Discussion on the non-clinical aspects

No new non-clinical studies were conducted with the fixed formulation compound. In view of the length and extent of clinical experience obtained with co-administration of commercially available PIOG and GLIM, the CHMP considered the omission of animal studies cited under indents 4.2.1 to 4.2.3 (a to f) inclusive of Annex 1 Directive 2001/83/EC is justified. GLIM studies were presented in the form of bibliographic references. In the case of carcinogenicity studies and genotoxicity studies no supportive studies or bibliographic references were provided. The company provided a CPMP opinion following an Article 10 referral for GLIM as supportive data for the justification of a lack of carcinogenicity and genotoxicity studies. The carcinogenic potential of PPAR agonists in general is of significant concern to regulators. Both PIOG and GLIM display PPARγ agonist activity. Due to the high protein binding of both PIOG (>98%) and GLIM (>99% in all species tested and >99.5% in humans) the applicant committed to evaluate the potential of the individual compounds to influence the individual free fractions and in the presence of such an interaction between PIOG and GLIM on the protein binding profile, to recalculate of the safety margins in relation to carcinogenic potential for both GLIM and PIOG based on plasma concentrations (AUCs) of the free fraction in relation to the proposed dosage regimens. The solution for these concerns was proposed to be handled as part of the follow up measures.

4. Clinical aspects

Introduction

This application is for a FDC, containing two authorized ingredients, pioglitazone hydrochloride and GLIM in two strengths: 30mg/4mg and 45mg/4mg tablets (initially for three strengths including also 30mg/2mg but this strength was withdrawn from the application by MAH). PIOG was originally authorized in the European Union in October 2000 and is currently authorised for use as monotherapy or as combination therapy with either MET or a SU in patients with T2DM. GLIM is a second generation SU originally authorised via the mutual recognition procedure in 1995. It is indicated to treat hyperglycaemia in patients with T2DM either as first-line monotherapy or as an add-on to MET or insulin. This application is submitted under Part B of the Annex to regulation 2309/93 and is a full "mixed" application in accordance with Article 8(3) and Annex I Part II.7 of Directive 2001/83/EC as amended. The data relating to PIOG is original data that fulfils 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 data previously assessed for the Community authorisations for PIOG were not resubmitted in this dossier. However, module 2 included an overview and summary of this data. A bibliographic review to describe the clinical profile of GLIM and SU class has been submitted for this application. The accepted indication for the PIOG/GLIM FDC is treatment of patients with type 2 diabetes mellitus who show intolerance to metformin or for whom metformin is contraindicated and who are already treated with a combination of pioglitazone and glimepiride.

Four clinical pharmacology studies are submitted with this application. These bioequivalence studies were completed to demonstrate that 3 initially proposed doses of the FDC are bioequivalent to the concomitantly administered individual tablets. Bioequivalence of the 30 mg/2 mg, 30 mg/4 mg, and 45 mg/4 mg doses were assessed in Study OPISU-001, Study OPISU-002 and Study OPISU-003, respectively. Additionally, the effect of food on the highest proposed dose of the FDC was determined during Study OPISU-004. These studies served to bridge the clinical safety and efficacy data for PIOG and GLIM or other SU used concomitantly as presented in this MAA to the FDC tablet. No studies of efficacy have been conducted with

the FDC. No studies with PIOG as add-on to GLIM therapy have been conducted either. Patients should be switched to a FDC only after the dosage of monotherapy has been optimized. The optimal dosage of GLIM is in the range of 4 mg. No scientific advice has been given in relation to this application. As this is a stand-alone application, summaries of all relevant PIOG and GLIM data are included and commented on, with emphasis on the pivotal data, which support the FDC.

GCP

The clinical trials were performed 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 in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

- Absorption

PIOG 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 PIOG. Single and multiple dose studies demonstrate linearity of pharmacokinetics in the therapeutic dose range. GLIM is completely absorbed (100%) after oral administration, with a significant degree of absorption occurring within the first post dose hour. Peak plasma concentrations generally occurs within 2 to 3 hours of oral dosing, but is delayed by approximately 12% when GLIM is administered with food.

- Bioequivalence studies

Study 01-04-TL-OPISU-001

This was a single-center, open-label, randomized, 2-treatment, 4-period, crossover, replicate-design study. Healthy subjects were randomly assigned to 1 of 2 treatment sequences in which they received a single oral dose of each treatment: AD-4833SU (PIOG 30 mg/GLIM 2 mg FDC product) and the concomitant administration of the commercially available PIOG 30 mg and GLIM 2 mg tablets. The sequences of treatments were such that upon completion of the study each subject had received both treatments twice. During each period, blood samples were collected at specified time points up to 72 hours posttreatment for the measurement of serum PIOG and GLIM concentrations. Adverse events (AEs) and concomitant medications were monitored and recorded throughout the study. Other safety evaluations included clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations. A total of 35 healthy subjects (mean age of 31.3 years), including 22 male and 13 female subjects, were randomly assigned to treatment at 1 study site. Thirty-two subjects (91.4 %), including 19 male and 13 female subjects, completed the study. Three subjects discontinued the study early: 2 subjects withdrew voluntarily and 1 subject withdrew because of AEs (mild facial lesions and mild dizziness).

Pharmacokinetic Results

The systemic exposures to PIOG and GLIM after administration of AD-4833SU were not considered to be bioequivalent to exposures observed after concomitant administration of the separate commercial PIOG and GLIM tablets. However, the 90% CIs of the LS mean ratios for AUC(0-inf) and Cmax of PIOG and AUC(0-inf), AUC(0-tlqc), and Cmax of GLIM were within the 80% to 125% interval. The 90% CI of the LS mean ratio for AUC(0-tlqc) of PIOG fell slightly below the 80% to 125% interval, as the 90% CI for this parameter was (77.48%, 87.17%). The LS mean and median Tmax values for PIOG were approximately 2 hours for both treatments, and the LS mean λz values were 0.079 1/hr after treatment with AD-4833SU and 0.068 1/hr after concomitant administration of the commercial tablets. The LS mean and median Tmax values for GLIM were between 2 and 2.6 hours for both treatments. The LS mean λz values were 0.103 1/hr after treatment with AD-4833SU and 0.128 1/hr after concomitant administration of the commercial tablets. According to CHMP the design of the study and analysis were appropriate and in accordance with regulatory guidance. The washout period of 7 days allows adequate time for elimination of both actives (>5 half-lives) thus avoiding a carry-over effect. The sampling times were appropriate and with sampling up to 72 hours post-dose, there was adequate data to calculate the exposure. There were minor administrative amendments to the protocol, which are not considered to impact on the validity of the study. Three subjects discontinued the study early for various reasons outlined above. One subject was excluded from the PK analysis in accordance with predefined criteria. However, exclusion of subjects for statistical reasons only in the opinion of CHMP was not acceptable. Analysis of all subjects' data should be provided unless there are clinical grounds for excluding a subject. The overall results provided demonstrate that the FDC tablet (PIOG 30mg/GLIM 2mg)

is bioequivalent with respect to rate and extent of exposure compared to the separate components available commercially.

Study OPISU-002 (PIOG 30 mg/GLIM 4 mg)

This was a single-center, open-label, randomized, 2-treatment, 4-period, crossover, replicate-design study. Healthy subjects were randomly assigned to 1 of 2 treatment sequences in which they received a single oral dose of each treatment: AD-4833SU (PIOG 30 mg/GLIM 4 mg fixed-dose combination product) and the concomitant administration of the commercially available PIOG 30 mg and GLIM 4 mg tablets. The sequences of treatments were such that upon completion of the study each subject had received both treatments twice. During each period, blood samples were collected at specified time points up to 72 hours posttreatment for the measurement of serum PIOG and GLIM concentrations. Adverse events (AEs) and concomitant medications were monitored and recorded throughout the study. Other safety evaluations included clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations.A total of 38 healthy subjects (mean age of 29 years), including 18 male subjects and 20 female subjects, were randomly assigned to treatment at 1 study site. Thirty-six subjects (94.7%), including 18 male subjects and 18 female subjects, completed the study. Two subjects discontinued the study early: 1 subject withdrew voluntarily for personal reasons, and 1 subject withdrew because of difficulties with the blood draws.

Pharmacokinetic Results

Systemic exposures to PIOG and GLIM after single-dose administration of AD-4833SU were bioequivalent to exposures observed after concomitant administration of the commercially available PIOG and GLIM commercial tablets. For PIOG and GLIM, the 90% CIs of the LS mean ratios for AUC(0-tlqc), AUC(0-inf), and Cmax were within the 80% to 125% interval. The LS mean and median Tmax values for PIOG were between 1.5 and 2.2 hours for both treatments. The LS mean λz values were 0.081 1/hr after treatment with AD-4833SU and 0.076 1/hr after concomitant administration of the commercial tablets. The LS mean and median Tmax values for GLIM were between 2.5 and 2.7 hours for both treatments. The LS mean λz values were 0.0755 1/hr after treatment with AD-4833SU and 0.0858 1/hr after concomitant administration of the commercial tablets. In the opinion of CHMP the design of the study and analysis were appropriate and in accordance with regulatory guidance. The washout period of 7 days allows adequate time for elimination of both actives (>5 half-lives) thus avoiding a carry-over effect. The sampling times were appropriate and with sampling up to 72 hours post-dose, there was adequate data to calculate the exposure. There were minor administrative changes and one significant amendment to the protocol, which are not considered to impact on the validity of the study. The amendment involved an increase in the sample size from 36 to 38 subjects. Two subjects discontinued the study early for reasons outlined above. One subject was excluded from the PK analysis in accordance with predefined criteria. However, exclusion of subjects for statistical reasons only in the opinion of CHMP was not acceptable. Analysis of all subjects' data should be provided. The overall results demonstrate that the FDC (PIOG 30mg/GLIM 4mg) is bioequivalent with respect to rate and extent of exposure compared to the separate components available commercially.

Study OPISU-003 (PIOG 45 mg/GLIM 4 mg)

This was a single-center, open-label, randomized, 2-treatment, 4-period, crossover, replicate-design study. Healthy subjects were randomly assigned to 1 of 2 treatment sequences in which they received a single oral dose of each treatment: AD-4833SU (PIOG 45 mg/GLIM 4 mg fixed-dose combination product) and the concomitant administration of the commercially available PIOG 45 mg and GLIM 4 mg tablets. The sequences of treatments were such that upon completion of the study each subject had received both treatments twice. During each period, blood samples were collected at specified time points up to 72 hours posttreatment for the measurement of serum PIOG and GLIM concentrations. Adverse events (AEs) and concomitant medications were monitored and recorded throughout the study. Other safety evaluations included clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations.A total of 36 healthy subjects (mean age of 31.5 years), including 15 male subjects and 21 female subjects, were randomly assigned to treatment at 1 study site. Thirty subjects (83.3 %), including 11 male and 19 female subjects, completed the study. Six subjects discontinued the study early: 3 subjects withdrew voluntarily and 3 subjects were withdrawn because of protocol violations (2 subjects had a positive urine drug screen and 1 subject failed to return for Period 3).

Pharmacokinetic Results

The systemic exposures to PIOG and GLIM after administration of AD-4833SU were bioequivalent to exposures observed after the concomitant administration of the separate commercial PIOG and GLIM

tablets. The 90% CIs of the LS mean ratios for AUC(0-inf), AUC(0-tlqc), and Cmax of PIOG and the AUC(0-inf) and AUC(0-tlqc) for GLIM were within the 80% to 125% interval. The 90% CI of the LS mean ratio for Cmax of GLIM fell slightly below the 80% to 125% interval, as the 90% CI for this parameter was (76.62%, 87.20%). For PIOG, the LS mean and median Tmax values were approximately 2 hours and the LS mean λz values were approximately 0.07 1/hr after both treatments. The LS mean and median Tmax values for GLIM were between 2 and 2.5 hours for both treatments. The LS mean λz values were 0.0848 1/hr after treatment with AD-4833SU and 0.104 1/hr after concomitant administration of the commercial tablets. Although the 90% CI for the Cmax of GLIM was slightly below the 80% to 125% interval at (76.6%, 87.2%), this finding is not considered clinically relevant. As described in detail in the Clinical Overview (Section 2.5), this conclusion is supported by the following: (1) the establishment of dose proportionality between the AD-4833SU tablets that contain 2 mg and 4 mg of GLIM, (2) the establishment of bioequivalence for the GLIM component of the 30 mg/4 mg dose of AD-4833SU, and (3) the nature of GLIM as a chronically administered drug. In the opinion of CHMP the design of the study and analysis were appropriate and were in accordance with regulatory guidance. The washout period of 7 days allowed adequate time for elimination of both actives (>5 half-lives) thus avoiding a carry-over effect. The sampling times were appropriate and with sampling up to 72 hours post-dose, there was adequate data to calculate the exposure. There were minor administrative amendments to the protocol, which are not considered to impact on the validity of the study. Six subjects discontinued the study early for various reasons outlined above. One subject was excluded from the PK analysis as he was inadvertently administered study drug according to the incorrect treatment sequence and this is acceptable. The overall results demonstrate that the fixed-dose combination tablet (PIOG 45mg/GLIM 4mg) is bioequivalent with respect to extent of exposure (AUC) compared to the separate components available commercially. However, the 90% CI for the Cmax of GLIM was slightly below the 80% to 125% interval at (76.6%, 87.2%), the applicant has put forward arguments as to why this finding is not considered clinically relevant. Considering these arguments and the fact that PIOG/GLIM is not intended for use under fasting conditions in clinical practice and that some decrease in Cmax with food is expected in any case, we can accept the arguments summarized above.

In conclusion in three bioequivalence studies, testing each of the combinations against the individual active substances, there were no major issues with the bioequivalence of GLIM. This shows the AUC s for all 3 strengths:

AUC_{0-t} (ng.h/mL)	**Point estimate**	**90% Confidence Interval**
30/2mg	0.99	0.95-1.04
30/4 mg	1.01	0.96-1.06
45/4 mg	0.96	0.93-1.02

However in the case of the PIOG component, shown below, bioequivalence was not shown for the 30mg/2mg combination (AUC_{0-t} 90% confidence intervals between 77.48 - 87.17).

AUC_{0-t} (ng.h/mL)	**Point estimate**	**90% Confidence Interval**
30/2mg	0.82	0.77-0.87
30/4 mg	0.87	0.83-0.91
45/4 mg	0.89	0.83-0.95

Such a difference was considered to be particularly significant in the way the FDC is ideally intended for use: that is for the individual dose of each component to be determined first before switching to the corresponding strength of the fixed combination product. Flexibility in applying the '80/125 CI guidelines' has been permitted occasionally where such differences are very small and clinical circumstances are such that these differences are irrelevant in practice. In the opinion of the CHMP it was not considered appropriate here. The whole rationale for using a combination of these two drugs is void if having arrived at the individual doses of each component for a patient; the appropriate fixed combination may not be relied upon

to have the same clinical effect. Since these two drugs are already available to be co-prescribed, there is no need to approve such licence applications with regulatory and clinical deficiencies. Therefore the Applicant committed to withdrawn the 30/2mg tablet from the Application.

- **Influence of food**

Study OPISU-004 Food-Effect Study
One single-centre, open-label, randomised, 2-period, crossover study was conducted to determine the effect of food on the absorption of PIOG and GLIM from the highest proposed dose of AD-4833SU (45 mg/4 mg). The food-effect study was designed so that 24 subjects would receive AD-4833SU 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 postdose for the measurement of serum PIOG and GLIM concentrations. Both treatments were separated by a 7-day washout period. Statistical analyses were performed on Tmax, λz, and natural logarithms of AUC(0-tlqc), AUC(0-inf), and Cmax of PIOG and GLIM. R^2 values for λz and the ratios of AUC(0-tlqc)/AUC(0-inf) were determined for each subject. If R^2 was less than 0.80 or if the ratio of AUC(0-tlqc) to AUC(0-inf) was less than 80% for an individual subject, then that subject's AUC(0-inf), λz, and T1/2 values were not included in the statistical analysis. The ANOVA model used in this study included fixed effects for sequence, period, and treatment and random effect for subject nested within sequence. Within the framework of this model, the 90% CIs for the ratio (test/reference) of the LS mean of AD-4833SU given under fed state (test) relative to the LS mean of AD-4833SU given under fasted state (reference) were calculated for AUC(0-inf), AUC(0-tlqc), and Cmax of PIOG and GLIM. The effect of food was determined by comparing these 90% CIs to the 80% to 125% interval. Data obtained from 23 subjects were sufficient to facilitate calculation of the pharmacokinetic parameters for both treatments and were included in the statistical analyses of AUC(0-tlqc), Cmax, and Tmax. Twenty-one and 23 subjects for PIOG and GLIM, respectively, had R^2 values for λz that were greater than or equal to 0.80 and AUC(0-tlqc) values that comprised more than 80% of the AUC(0-inf) value, and therefore, were included in the statistical analysis of AUC(0-inf). The results from this study indicate that systemic exposure to PIOG and GLIM were not altered by the presence of food. The 90% CIs of the LS mean ratios for AUC(0-inf) of PIOG and AUC(0-inf) and Cmax of GLIM were within the 80% to 125% interval. Dosing with food did result in a significant prolongation in the LS mean Tmax of PIOG from approximately 1.6 to 3.6 hours (median=1.5 to 4 hr). This food-induced delay in Tmax was associated with a 9% decrease in the LS mean value for the Cmax of PIOG. The 90% CI of the LS mean ratio for Cmax of PIOG fell slightly below the 80% to 125% interval, as the 90% CI for this parameter was (79.39%, 105.46%). In the opinion of CHMP the design of the study and analysis were appropriate and were in accordance with regulatory guidance. The washout period of 7 days allows adequate time for elimination of both actives (>5 half-lives) thus avoiding a carry-over effect. The sampling times were appropriate and with sampling up to 72 hours post-dose, there was adequate data to calculate the exposure. The study shows findings consistent with what is known about the effect of food on the individual components. The rate of absorption of PIOG was slowed but overall exposure was unchanged. While a slight food effect has been reported in the literature for GLIM, the extent of this effect in this study was not statistically significant.

In conclusion the 90% CI for the Cmax of GLIM was outside the 80% to 125% interval (76.6%, 87.2%) in the study comparing the 45mg/4mg strength. However, this is unlikely to be clinically relevant. In a food effect study conducted with the highest strength proposed for marketing, a modest food effect was seen for GLIM as would be expected and the rate of absorption of PIOG was slowed which is consistent with the SPC of PIOG.

- Distribution

The volume of distribution of PIOG is small with a mean of 0.253L/kg. PIOG is extensively bound to plasma proteins. GLIM is more than 90% bound to serum proteins, mainly to albumin. The degree of protein binding is important because the unbound portion of the drug determines the pharmacokinetic profile. Conditions that alter the normal protein binding of the drug will alter the pharmacokinetics and affect the occurrence of side effects that are concentration dependent. Second generation SU, of which GLIM is one, are approximately 100 times more potent than first generation SUs. Despite having shorter half lives, which range from 3 to 5 hours compared to 24 to 48 hours with the first generation compounds, second generation SUs can typically be dosed once daily. The half-life of GLIM is 5 hours after single oral dosing and increases to approximately 9 hours after multiple dosing.

- Elimination

PIOG 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. 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 PIOG is negligible. The profile of metabolites of PIOG in diabetic patients is similar to that seen in healthy volunteers.

Unlike the earlier developed SUs, GLIM is extensively metabolised rather than excreted. The principal hepatic isoforms involved in the metabolism of GLIM is CYP2C9. The metabolites are excreted in urine, with M1 accounting for approximately 60% of the administered dose; the remainder is found in faeces in the form of the M2 metabolite. M1 has approximately 30% of the pharmacologic activity relative to the parent compound, the clinical significance of which has not been established. GLIM does not accumulate in serum, and its pharmacokinetic behaviour does not differ between healthy subjects and patients with T2DM or with hepatic dysfunction, age, or gender. However, decreased renal function is associated with increased drug distribution and clearance. Potential interactions may occur between GLIM and other drugs that are metabolised by CYPC9, such as phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid.

- Dose proportionality and time dependency

Dose proportionality of PIOG and the main metabolites (Total Active Compounds) was demonstrated over the dose range of 2 to 60 mg in both single- and repeated-dose studies conducted in Japan and the United States. Prescribing information for GLIM [6] summarised the pharmacokinetic parameters observed in a single-dose crossover study of the drug when given to 48 healthy subjects in 4 different doses. Mean (±SD) peak plasma concentrations were 103 (±34) ng/mL, 177 (±44) ng/mL, 308 (±69) ng/mL, and 551 (±152) ng/mL at doses of 1, 2, 4, and 8 mg, respectively. Data indicate dose-proportional PK within the therapeutic range of doses for PIOG and GLIM.

- Special populations

  - Impaired renal function

Cmax and AUC of PIOG and metabolites M-III and M-IV were decreased in subjects with impaired renal function. T1/2 was generally unaffected. PIOG and metabolites M-III and M-IV did not appear to accumulate in subjects with renal impairment after repeated doses. The urinary excretion of the metabolites was not quantified, but the urinary excretion profile of the metabolites appeared to be the same as in subjects with normal renal function. The apparent lower C_{max} and AUC values in subjects with impaired renal function may be due to reduced plasma protein levels, which are often observed in individuals with renal impairment. As the drug is eliminated primarily by oxidation in the liver, the intrinsic clearance is presumably unaffected. Pharmacokinetic theory predicts that in this situation, despite the difference in total concentration, the free (ie, therapeutically relevant) drug concentrations will be similar in patients with normal versus impaired renal function. There is therefore no need for dose adjustment in patients with renal failure. Rosenkranz et al analysed the pharmacokinetics and safety of GLIM in patients with type 2 diabetes who had renal impairment and a creatinine clearance level above 10 mL/min at Baseline. Fifteen patients who received a single dose of 3 mg GLIM underwent serial blood and urine sample testing over 24 hours. Sixteen patients who received a dose of 1 to 8 mg GLIM to achieve glucose control over a 3-month period underwent serum and urine pharmacokinetic testing on the first and last days of the study. The patients in this study were placed into 1 of 3 groups according to their creatinine clearance levels. Five patients had creatinine clearance levels of 77.7 mL/min; 3 patients had levels of 27.7 mL/min; and 7 patients had levels of 9.4 mL/min. Results of the single-dose, open-label study indicated that serum levels of GLIM decreased with a decline in renal function. Nevertheless, mean AUC levels of the M1 and M2 metabolites rose 2.3 and 8.6 times in the 2 groups of patients with higher creatinine clearance levels. The apparent terminal half-life for GLIM remained the same regardless of renal function. The half-lives for both metabolites increased as renal function declined. The mean level of urinary excretion of the metabolites as a percent of dose decreased to 44.4% for patients in the first group, 21.9% for patients in the second group, and 9.3% for patients in the third group. Findings from the multiple-dose study were consistent. Tandemact is contraindicated in severe renal function disorders.

- Impaired hepatic function

PIOG and GLIM are contraindicated in patients with hepatic impairment and the proposed SPC for Tandemact has a contraindication also.

- Gender

Three single dose studies consistently showed that female subjects have higher Cmax and AUC values and delayed Tmax results for PIOG. With the exception of Cmax, there was a less evident gender effect on the pharmacokinetic parameters for Total Active Compounds. Part of the higher Cmax and AUC values observed in female subjects may be due to their lower body weight. The data from studies in diabetic patients appeared less consistent as to whether a gender difference existed and suggested that a possible gender difference may not be relevant in clinical practice. For GLIM, after adjusting for body weight, pharmacokinetic patterns are similar for men and women.

- Race

There was no formal study conducted on the influence of ethnicity on the pharmacokinetics of PIOG. However, the open-label, single-dose, 2-way crossover study on the bioequivalence of three 15 mg tablets compared to one 45 mg tablet included 12 Caucasian male subjects and 11 Black male subjects (PNFP-018). Comparison of the pharmacokinetics of Black and Caucasian subjects in this study gave an indication of existing major ethnic differences in the pharmacokinetics of PIOG. For all pharmacokinetic parameters the 90% confidence intervals include 100%, thus suggesting that there are no major differences in the absorption and disposition of PIOG between Black and Caucasian subjects. In summary, considering the metabolic pathways of PIOG, major ethnic differences in PIOG pharmacokinetics are not expected. In support of this, the data presented here did not suggest clinically relevant differences in the pharmacokinetic behavior of PIOG based on ethnicity. Although pharmacokinetic studies have not been conducted to evaluate the disposition of GLIM in racial ethnic groups, placebo-controlled clinical studies have documented comparable glucose-lowering effects in Caucasians (n= 536), Blacks (n=63), and Hispanics (n=63). The CHMP agree with the position of the company: there are no SPC comment warranted.

- Weight

In individual paper by U. Shukla et al compared pharmacokinetic characteristics in patients with type 2 diabetes who were morbidly obese and those who had normal weight. Serum concentrations of GLIM and its metabolites were measured in 14 patients of normal weight and 14 obese patients who received a single oral dose of GLIM 8 mg after an overnight fast. Mean peak concentration, time to reach peak concentration, AUC, terminal half-life, and relative total clearances were equivalent in the 2 groups. Although morbidly obese patients excreted significantly greater amounts of M1 ($p=0.0430$) and M2 ($p=0.0051$) than normal-weight patients, these differences were not considered to be clinically relevant because the metabolites do not have meaningful pharmacologic activity. Differences in PIOG PK between men and women have been partly attributed to differences in weight. However, no specific dose adjustment for weight is required for PIOG and none is considered necessary for Tandemact.

- Elderly

Two studies were performed to assess possible age-related differences in the pharmacokinetics of PIOG. In comparison with the pharmacokinetic parameters of PIOG and "Total Active Compounds" obtained with the non-elderly healthy adult subjects, C_{max} and AUC in elderly Japanese subjects on the 30mg/day treatment were slightly lower, but the other pharmacokinetic parameters did not show any marked differences. The composition of metabolites in the serum at steady state was almost the same for elderly and non-elderly healthy volunteers. Adjusting apparent lower urinary excretion rates in the elderly at the 30mg dose for the lower AUC levels in the elderly, there was almost no statistically significant difference between the excretion rates in the non-elderly healthy adult subjects and those in elderly subjects. Steady state results suggest that PIOG does not accumulate in elderly subjects on repeated dosing. In a US elderly population AUC of PIOG was increased by about 20% compared to non-elderly, with a slightly lower clearance. In summary, the Japanese study indicates lower C_{max} and AUC values of PIOG in elderly subjects, while the metabolism and excretion of PIOG appears to be similar to young adult subjects. The US study indicates increased AUC levels of PIOG and Total Active Compounds in elderly subjects as compared to middle-aged subjects, and slower elimination of PIOG in elderly subjects. These apparent contradictory results suggest that, depending on the study population, minor differences in pharmacokinetics between elderly and non-elderly subjects may exist, but the differences are not clinically relevant. Age does not appear to affect the pharmacokinetics

of GLIM. Prescribing information for GLIM (2003 USA) reported the results of a study that compared pharmacokinetics in patients over and under the age of 65 who received 6 mg GLIM daily for type 2 diabetes. Pharmacokinetic profiles were similar in the 2 age groups. The mean AUC at steady state was 13% lower for elderly patients than for younger patients. Mean weight-adjusted clearance was 11% higher in elderly patients than in younger patients. The European SPC also states that PK of GLIM are similar in young patients and in the elderly (over 65 years).

- Children

Pharmacokinetic data in the paediatric population are not available for PIOG and GLIM but in the opinion of the Committee Tandemact is not intended for use in children and therefore this is satisfactory.

- Pharmacokinetic interaction studies

Drug interaction studies indicate that PIOG does not induce or inhibit the metabolism of drugs cleared by the P450 system. Further drug interaction studies conducted since 1999 do not indicate a potential interaction between CYP3A4 substrates or a potent inhibitor, ketoconazole. PIOG did not affect the steady state pharmacokinetics of SUs. Potential interactions may also occur with highly-protein bound drugs. This is adequately reflected in the SPC.

Pharmacodynamics

PIOG/GLIM combines 2 antihyperglycaemic agents with different mechanisms of action to improve glycaemic control in patients with T2DM. No new pharmacodynamic studies were submitted for PIOG not for the FDC. The literature on SUs in general and on GLIM specifically has been summarised and appears adequate. A summary of the two actives pharmacodynamic effects is provided.

PIOG is a thiazolidinedione and a potent and highly selective agonist for the nuclear receptor PPARγ. PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ receptors modulate the transcription of a number of insulin-responsive genes involved in the control of glucose and lipid metabolism. These 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 PIOG in diabetic subjects have shown that once-daily administration of PIOG 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 PIOG suggests that PIOG 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 PIOG has no direct stimulatory effect on the beta cells of the pancreas.

Like other SUs, GLIM stimulates or potentiates the release of insulin. In contrast with glibenclamide, which binds to the 140kDa subunit of the SUR, GLIM binds to the 65kDA subunit of the SUR, and it acts on the ATP-sensitive potassium channel that resides in the pancreatic beta-cell plasma membrane. GLIM also stimulates extrapancreatic effects, as shown by an increased sensitivity of peripheral tissues to insulin in animal and clinical studies. In addition, elevated postprandial insulin and C-peptide responses and enhanced glycaemic control have occurred in the absence of clinically relevant increases in fasting insulin and C-peptide levels in long-term randomised and placebo-controlled clinical trials. Decreases in blood glucose levels are dose dependent, with no difference in response whether administered as a single dose or in divided doses. Pharmacodynamic effect is not affected by age, ethnicity, weight, or gender. The risk for hypoglycaemia has been lower for GLIM than for other SU. A review of 21 clinical trials reported treatment-emergent signs and symptoms for more than 4200 patients who had been treated with GLIM. This review determined the cumulative incidence of signs and symptoms of hypoglycaemia for clinical trials conducted in the United States and Europe. The cumulative incidence of hypoglycaemia was 13.9% among patients who had been treated with GLIM and 2.0% in patients who had received a placebo in placebo-controlled United States (US) clinical studies. The incidence was 10.0% for patients who had received GLIM in comparison with 16.3% for patients who had received glibenclamide in glibenclamide-controlled US clinical studies. Pooled data from European clinical studies indicated that the cumulative incidence of signs

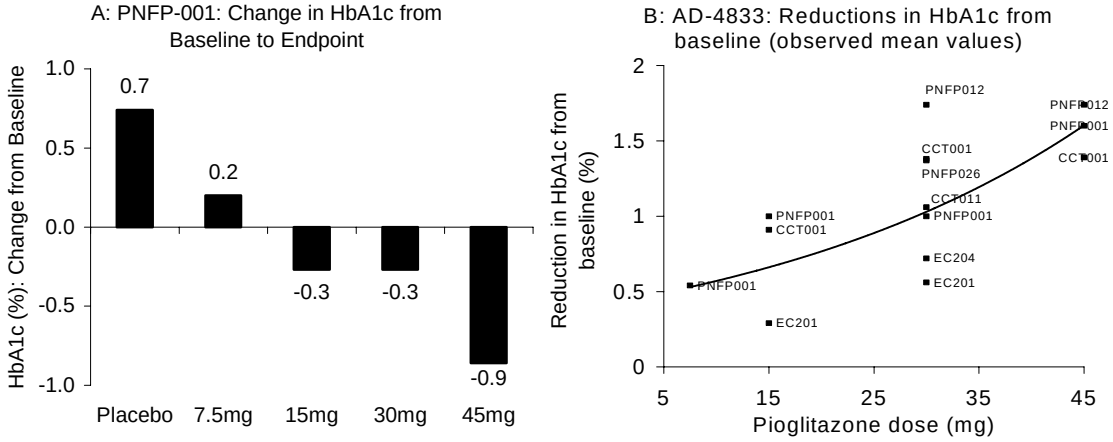
and symptoms of hypoglycaemia was 3.0% in patients who were treated with GLIM, 2.2% in those who received glibenclamide, and 6.1% in those who were treated with gliclazide. The review paper concluded that the differences in results for the US and European studies may be due to variations in the design and reporting of the findings.

Clinical efficacy

- Dose response studies

A number of placebo-controlled studies with PIOG as monotherapy have been performed and submitted as part of the 1999 MAA. Figure 1 shows the reductions from baseline (placebo adjusted) of glycosylated haemoglobin (HbA_{1c}) in the major dose-ranging study performed (PNFP-001) and throughout the worldwide program of all studies that were 12 weeks or more in duration.

Figure 1. Summary of Glucemic Control Results from the pivotal Placebo-Controlled PIOG Monotherapy Study (PNFP-001, Submitted with 1999 ISE).



A: Change in HbA_{1c} (%) from Baseline to Week 26.
B: Placebo adjusted reduction in HbA_{1c} in worldwide phase 2 and 3 programme using PIOG 7.5, 15, 30, and 45 mg.

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. These improvements in glycaemic control with PIOG in placebo-controlled studies were generally achieved with reductions in insulin and C-peptide. Furthermore, during dynamic testing (oral glucose tolerance tests; OGTT), PIOG was found to reduce glucose excursion following a glucose load with minimal effects on insulin levels. Review papers by R. Campbell, M. Korytkowski, and A. McCall reviewed a placebo-controlled study of 304 patients with type 2 diabetes who received randomised treatment of 1 mg, 4 mg, or 8 mg GLIM. The median change in FPG in comparison with placebo was 43 mg/dL in patients who received 1 mg glimperide, 70 mg/dL in patients who received 4 mg of the drug, and 74 mg/dL in patients who received 8 mg. Changes in HbA_{1c} were 1.2%, 1.8%, and 1.9% for the 1 mg, 4 mg, and 8 mg doses, respectively. Results of this study indicated a dose response up to 4 mg, and it concluded that the 4 mg dose appears to be nearly maximally effective. The authors of the study concluded that the 8 mg dose might be suitable for patients who have HbA_{1c} levels greater than 8% (Campbell 1998; McCall 2001). A review paper by R. Perfetti et al reported that dose-ranging clinical studies show that the 8 mg dose of GLIM produces the maximum biologic effect, and the optimal response tends to occur within 3 weeks of the start of treatment. One clinical trial summarised by Perfetti concluded that 69% of patients who had failed nonpharmacologic treatment for type 2 diabetes were able to achieve an HbA_{1c} level below 7% when treated with GLIM (Perfetti 2000). The dose response-patterns shown by GLIM are similar to those exhibited by other SU drugs. These patterns show that lower doses of sulphonyureas produce the most effect on hyperglycaemia, and that half of the maximum dose of the drugs provides all of the long-term effect on glycaemic control (McCall 2001). There is adequate evidence of dose-response effects for PIOG within the range 15-45mg per

day and for GLIM at doses of 1-4mg per day. The maximally effective dose of GLIM is 8mg per day but most of the effect is seen at half the maximal dose. The SPC for GLIM suggests 6mg as the maximum dose but only in exceptional cases.

- Main studies

No studies of efficacy have been conducted with the FDC. No specific studies of PIOG as add-on to GLIM therapy have been conducted either. The efficacy of the combined use of PIOG with a SU (several agents were in use, among them GLIM) was demonstrated in 3 previously submitted controlled clinical trials: Study PNFP-010, Study PNFP-341 and Study EC409. This led to the expansion of PIOG indications to include an add-on indication to SU when glycaemic control was inadequate with maximal tolerated SU monotherapy and when MET was contraindicated or not tolerated.

Overview of PIOG plus SU combination therapy studies.

Study	Duration	Treatments (a)	Patients (ITT)	Critical Design Features
EC409	104 weeks	PIOG 15-45 mg + SU	315	Dose-titration (tolerability based) Change from Baseline analysis
		MET 850-2550 mg + SU	313	
PNFP-341	24 weeks	PIOG 30 mg + SU	351	Fixed dose
		PIOG 45 mg + SU	351	
PNFP-010	16 weeks	Placebo + SU	187	Fixed dose
		PIOG 15 mg + SU	184	
		PIOG 30 mg + SU	189	

Source: EC409, Appendix 16.1.9.1, Table 2; PNFP-341, Appendix 15, Table 3.1.R; PNFP-010, Appendix 15, Table 3.1.
(a) In EC410 the comparator drugs were titrated to maximal tolerated dose.

Study PNFP-010

The objective of this study was to compare administration of placebo, 15 mg and 30 mg of PIOG in patients with T2DM who did not have adequate glycaemic control despite being on a stable SU dosing regimen. The length of the maintenance phase of the study was 16 weeks as suggested in the CHMP Clinical Investigation of Diabetes NfG document. The NfG document also suggests that patients who are included do "*not need any change and/or adjustment in previous medication during the 8 to 12 weeks preceding the study to ensure the maximal effect of the previous medication has been observed"*. Some patients had a one week placebo run-in period in addition to the 30 days on stable SU monotherapy as an inclusion criteria. Of 560 patients randomised, 187 were in the placebo group, 184 in the 15 mg PIOG group and 189 in the 30 mg PIOG group. 30(16%) patients withdrew in the placebo group, 29 (16%) in the 15 mg PIOG group and 23 (12.2%) in the 30 mg PIOG group.

Results

There were significant reductions from baseline in HbA1C for both groups where PIOG was given with a SU (-0.82 and -1.22), whilst there was a small increase of 0.065 with placebo. Treatment with either dose of PIOG (15 or 30 mg) plus a SU resulted in statistically significant ($P \leq 0.05$) mean decreases from Baseline in HbA_{1c} and FPG at each time point throughout the study. The differences in mean HbA_{1c} and FPG between the placebo plus SU and PIOG plus SU groups in mean change from Baseline were statistically significant ($P \leq 0.05$) at all time points. The proportion of subject who responded to treatment was substantially higher in both PIOG dose groups (56.8% and 74.2%) than in the placebo group (23.8%) for HbA_{1c}. At Endpoint (Week 16), the difference in LS mean change from Baseline in HbA_{1c} between each dose of PIOG plus SU and placebo plus SU was -0.88% (95% CI; -1.17, -0.58) for the PIOG 15 mg plus SU group and -1.28% (95% CI; -1.57, -0.99) for the PIOG 30 mg plus SU group. For FPG, the difference in LS mean change from Baseline was -2.19 mmol/L (95% CI; -2.86, -1.57) for the PIOG 15 mg plus SU group and -3.21 mmol/L (95% CI; -3.32, -2.55) for the PIOG 30 mg plus SU group.

Study PNFP-341

The design of this study was similar to study PNFP-010 except for patients on a stable SU treatment regimen being randomised to 30 mg or 45 mg of PIOG, and there being no placebo comparator. In this study, 702

patients were randomised, 351 to each treatment group. 84 (23.9%) patients in the 30 mg PIOG group withdrew compared to 97 (27.6%) in the 45 mg PIOG group.

Results

In this study the patients receiving a SU and 30mg PIOG showed a significant reduction from baseline in HbA1C of 1.55% compared with 1.64% for patients receiving a SU and 45mg PIOG. At Week 24, an incrementally larger decrease in HbA_{1c} was seen with 45mg, although the difference was not statistically significant (LS mean difference: -0.12 [-0.36, 0.12]). The effects observed with PIOG on glycaemic control were supported by the findings on fasting plasma glucose with significant reductions from Baseline to Week 24 observed with both 30 and 45 mg. HbA_{1c} responder rates (≥0.6% reduction from Baseline or ≤ 6.1% at Endpoint) fasting plasma glucose responder rates (responder: ≥ 30mg/dL reduction from Baseline) were higher with 45 mg compared with 30 mg PIOG. Lipid profile was improved by both 30 and 45 mg PIOG with reductions observed in triglycerides, VLDL-cholesterol, and FFAs and increases in HDL-cholesterol. Small increases from Baseline of less than 5% in LDL-cholesterol and TC were observed with both the 30 and 45 mg PIOG groups.

Study EC409

The third study evaluated the benefit of adding either PIOG or MET to treat patients with T2DM who were currently being treated with a SU at 50% maximum or greater of the recommended dose for at least three months. Eligible patients were randomised to receive PIOG or MET for 104 weeks in addition to their SU therapy. Patients were initially seen every four weeks during a forced titration period where the dose of study drug was increased at each visit from 15-30mg and then 30-45 mg of PIOG or 850mg od (once a day) to 850mg bd (twice a day) and then from 850mg bd to 850mg three times a day of MET. A total of 315 and 313 patients were analysed in the PIOG and MET treatment groups, respectively.

Results

The analysis after 104 weeks of treatment showed a 1.03% reduction in HbA1c levels with PIOG compared to 1.16% on MET which gives a between treatment difference of 0.13% with corresponding 95% confidence interval of -0.06 to 0.31%. This is very similar to the week 52 results where a 1.2% reduction in HbA1c levels with PIOG compared to 1.36% on MET which gives a between treatment difference of 0.15% with corresponding 95% confidence interval of -0.01 to 0.32%. In the PIOG group, 72% of patients completed 2 years of treatment compared with 78% in the MET group. Adverse events and lack of efficacy accounted for approximately half of the withdrawals. After 2 years treatment on top of SU, both PIOG and MET had achieved a 1% decrease in HbA_{1c} without the addition of any further agents; 1.03% with PIOG and 1.16% with MET. This represents a difference of 0.13% (-0.06, 0.31) between the groups.

These three studies provide evidence of clinically significant improvement in glycaemic control with the addition of PIOG 15-45mg to SU treatment in a typical T2D population.

- Analysis performed across trials (pooled analyses and meta-analysis)

A comparison of the three studies which are considered pivotal to support the combination use of PIOG and GLIM is provided in section 2.7.3.3.3 of module 2 and is summarised here.

All studies included both men and women. A summary of the entry criteria for the 4 studies is presented in table below.

	EC409	PNFP-341	PNFP-010
Age (yr)	≥35 to ≤75	≥18 years	30 to 75
Period on existing antidiabetic medication	3 months (maximum tolerated or ≥50% maximum dose)	Fixed dose of SU for ≥30 days prior to Visit 1	Fixed dose of SU for ≥30 days prior to enrolment
Previous antidiabetic medication prohibited	TZD, MET, or insulin (short-term use was allowed)	TZD or insulin (chronic use within 4 months of study)	Insulin (chronic use within 4 months of study)
BMI (kg/m^2)	≥25 to ≤ 45	≥25 to ≤45	25 to 45
HbA_{1c} (%)	≥7.5% to ≤ 11.0%	≥8.0%	≥8.0%
Fasting C-peptide (ng/mL)	≥1.5 ng/mL	Not specified	≥1 ng/mL

Source: EC409 CTR, Sections 9.3.1 and 9.3.2; PNFP-341 CTR, Sections 9.3.1 and 9.3.2; PNFP-010 CTR, Sections 7.3.1 and 7.3.2.
TZD = thiazolidinedione, SU = SU.

In general, demographics and baseline characteristics were well matched across the studies. Whilst most patients (98%) in study EC409 were Caucasian, more non-Caucasian patients appeared in studies PNFP-341/PNFP-010 (67% and 79%, respectively). Patients in the US studies PNFP-341/PNFP-010 had higher HbA_{1c} and FPG compared to EC409. No formal meta-analysis of the data from the 3 studies has been performed since the data have all been submitted previously and the studies are different in design with respect to objectives and duration of treatment such that 'grouping' of data is not appropriate. For all 3 studies the primary efficacy measure was the change in HbA1c from Baseline to last value. These data show that doses of 30 and 45 mg PIOG are effective in improving glycaemia when concomitantly administered with SU. The data also suggest that peak effect may not be seen until 6 months treatment as in PNFP-341 and that these effects are maintained to 2 years as observed in EC409. In all studies, glycaemic control was further improved following addition of PIOG to SU therapy, at doses up to 45 mg daily. PNFP-010 was a short placebo-controlled study, which showed the benefit of adding 30 mg PIOG with an absolute decrease from Baseline in HbA1c at 16 weeks of 1.22% compared with an absolute increase in placebo of 0.06%. In study PNFP-341, both 30 and 45 mg showed significant absolute decreases from Baseline in HbA1c of 1.55% and 1.64%, respectively, after 24 weeks treatment. This level of improvement was similarly found in study EC409, which compared the addition of PIOG with that of MET to an established SU regimen. PIOG plus SU and MET plus SU treatments resulted in absolute mean adjusted decreases from Baseline in HbA1c of 1.22% and 1.39%, respectively (treatment-group difference is not statistically significant [95% CI on mean difference: -0.06,0.31]). Decreases in fasting plasma glucose ranged from approximately 1.9 to 2.9 mmol/L in PIOG groups and were found to be statistically significantly greater than those observed with placebo after 16 weeks (2.88 mmol/L) and MET after 2 years (2.0 mmol/L). Glycaemic responder rates are summarised in table below. The responders were defined different in study EC409 and different in studies PNFP-341 & PNFP-010 (EC409: reduction in HbA1c of greater than 0.6%; PNFP-341 & PNFP-010: HbA1c responder was any patient whose HbA1c reduced to less than or equal to 6.1% or decreased from Baseline by greater than or equal to 0.6%).

HbA_{1c} and FPG Responder Rates to PIOG as Combination Therapy with Existing SU Treatment

	EC409 (a)		PNFP-341 (b)		PNFP-010 (b)	
	Pio+SU	Met+SU	30mg+SU	45mg+SU	Pbo+SU	30mg+SU
HbA_{1c} responder rate (%)	64.1	70.3	77.4	79.5	23.8	74.2

Pio=PIOG, SU=SU, Met=MET, 30 mg=30 mg PIOG, 45 mg=45 mg PIOG, Pbo=placebo.
(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%.

Responder rates demonstrate that PIOG, as combination therapy with SU, effectively improved glycaemic control in at least 64% of patients treated and that the proportion of patients that respond to therapy is comparable to that seen with the commonly used combination of MET and SU. In order to qualify for entry to these studies, patients had to be on a stable dose of a SU agent and in the case of study EC409, the dose had to be at least 50% of the maximum dose for that agent or at the maximum tolerated dose. Improved glycaemic control was evident with doses of PIOG from 15 to 45mg added to a SU and efficacy was

maintained for 2 years as shown in study EC409. The PIOG indications were varied in 2004 on the basis of these studies. As no new studies have been conducted with PIOG and GLIM or other SU, there does not seem to be any basis to support further widening of the population for whom PIOG could be prescribed.

- Clinical studies in special populations

A pediatric development program for this medicinal product is not proposed and this is acceptable, given the proposed indication, which is primarily a condition of adults.

- Supportive studies

Studies of PIOG as monotherapy are considered as supportive in the context of this application. In 1-year studies, PIOG improved glycaemic control similarly to MET and gliclazide. Furthermore, PIOG showed additional benefits on a number of secondary endpoints in these studies such as reductions in plasma insulin, improvements in insulin sensitivity and response to a glucose load, improvements in lipid profile, and established cardiovascular risk markers. In general, these improvements were found to be at least as good or better than those observed with MET or gliclazide. PIOG showed good maintenance of effect up to 1 year reaching a maximum HbA_{1c} reduction by Week 32 and increasing from the nadir by less than 0.2% in studies EC404 and EC405. This was also the case with MET; however, gliclazide reached maximum HbA_{1c} reduction by Week 24 and by Week 52, HbA_{1c} had increased from the nadir by 0.41% indicating a loss of glycaemic control. FPG was also well maintained with PIOG and MET where maximum response was seen by Week 24 and increased very little thereafter; 0.3 mmol/L for PIOG and 0.4 mmol/L for MET. With gliclazide, maximum reduction in FPG was seen at Week 16 and increased thereafter by 1.0 mmol/L to Week 52. The results of the supportive PIOG studies are concordant with the pivotal studies and support the use of PIOG at doses of 15-45 mg daily, titrated according to response, in the treatment of type 2 diabetes.

An individual paper by G. Scholz et al summarised the results of a study with 22,045 patients with type 2 diabetes for whom GLIM would be administered as first-line therapy (either no previous treatment or treatment with diet alone) or second-line therapy (previous treatment with another antihyperglycaemic drug, oral or insulin) with GLIM added to or replacing the current antihyperglycaemia therapy. The study involved 22,045 patients with type 2 diabetes and had an 8-week treatment period. Patients received an initial dose of 1.6 mg GLIM. The dose was increased to a mean of 2.2 mg over the period of the study. In patients who were treated initially with GLIM, HbA_{1c} levels declined by a mean of 1.8%. The absolute mean reduction in HbA_{1c} levels was 1.3% in patients whose therapy was changed to GLIM. The reduction in HbA_{1c} levels was greater in patients who were treated with GLIM exclusively. The decline was 1.5% in these patients compared with 1.3% in patients who had received GLIM as add-on therapy to a pre-existing antihyperglycaemic regimen (Scholz 2001).

- Discussion on clinical efficacy

This application was for a FDC, containing two authorized ingredients, pioglitazone hydrochloride and GLIM in two strengths: 30mg/4mg and 45mg/4mg tablets (initially for three strengths including also 30mg/2mg but this strength was withdrawn from the application by MAH). Four clinical pharmacology studies were submitted with this application. These bioequivalence studies were completed to demonstrate that 3 initially proposed doses of the FDC are bioequivalent to the concomitantly administered individual tablets. Bioequivalence of the 30 mg/4 mg and 45 mg/4 mg doses were proven however the applicant failed to demonstrate the bioequivalence of the 30mg/2mg tablet and withdrawn it from the application. The bioequivalence studies served to bridge the clinical safety and efficacy data for PIOG and GLIM to the FDC tablet. No studies of efficacy have been conducted with the FDC. No studies with PIOG as add-on to GLIM therapy have been conducted either. Patients should be switched to a FDC only after the dosage of monotherapy has been optimized. The indications for Tandemact were modified as to reflect the need to titrate patients with optimal doses of individual components of the combination before switching to FDC. Tandemact is indicated for the treatment of patients with type 2 diabetes mellitus who show intolerance to metformin or for whom metformin is contraindicated and who are already treated with a combination of pioglitazone and glimepiride. No scientific advice has been given in relation to this application.

Clinical safety

The safety data from the healthy subjects in the phase I studies referred to above were not designed to characterise the adverse event profile for the combination product. The applicant utilises the data from the 3 previously submitted controlled clinical trials (Studies PNFP-010, PNFP-341, and EC409), even though

these are based on the co-administration of the individual constituents. The applicant has also submitted safety data for PIOG and GLIM when used as monotherapy, safety data based on literature review and postmarketing safety information for PIOG.

- Patient exposure

PIOG

A total of 3211 patients were randomly assigned to treatment and received at least 1 dose of study drug in 6 PIOG monotherapy studies (EC404, EC405, GLAB, GLAE, ATS-K001, EC415). Of this total, 1653 received PIOG. In studies EC404, EC405, GLAB, and GLAE a high percentage of patients receiving either treatment completed the studies (between 84% and 97% of patients who received PIOG and between 84% and 92% of patients receiving the comparator agent). Fewer patients in either treatment group completed the ATS-K001 and EC415 studies. In study ATS-K001, 76% of patients receiving PIOG compared to 58% of patients receiving acarbose and in EC415, 54% of patients receiving PIOG and 43% of patients receiving gliclazide completed the protocols. The demographics within each study were typical for a type 2 diabetic population. The PIOG monotherapy study populations reported a high proportion of concomitant cardiac and vascular disease and taking anti-hypertensive and cardiac medication. High incidences of vascular disorders (mainly hypertension), other metabolic and nutritional disorders, cardiac disorders, and eye disorders were reported in each of the PIOG monotherapy studies. As is usual in a relatively elderly population, musculoskeletal disorders (mainly arthritis) were also commonly noted as concomitant diseases.

PIOG Plus SU Combination Therapy

A total of 1,901 patients were enrolled in the studies. Of this total, 1,394 received PIOG as combination therapy with SU. The remaining patients received SU plus a comparator agent (either MET or placebo). More than 70% of PIOG patients included in EC409 completed 2 years of treatment. The duration of treatment ranged from 16 to 104 weeks in the combination therapy studies. Dosing regimen for PIOG was 30 or 45 mg once daily (od), with the exception of the first portion of EC409, which had a forced dose-titration period during which subjects could initiate treatment at 15 mg.

GLIM

A review paper by McCall has reviewed clinical trial data in over 5000 patients in the United States and Europe, 3500 of whom received GLIM in doses ranging from 1 to 32 mg per day over 2 weeks to more than 2 years.

- Adverse events/Serious adverse events

PIOG

Over 2 years of treatment, PIOG treatment is associated with a similar incidence of AEs to other oral hypoglycaemic agents. Withdrawals due to AEs, SAEs and fatal SAEs also showed similar incidences with PIOG treatment and treatment with other oral hypoglycaemic agents. Analysis of the most commonly reported AEs showed some variation between different trials as would be expected. Across all the trials, however, the only AEs which were consistently reported at higher rates with PIOG compared to non-PIOG treatment were oedema and weight increase. These are known effects of PPARγ agonists and are detailed in the SPC. The absolute incidence of reports of oedema varies a little between trials but overall incidence of oedema is about two to three times greater than that reported for other oral hypoglycaemic agents. In active comparator groups, gastrointestinal AEs were reported more often with MET than PIOG. The reporting rates of SAEs were similar for PIOG treated patients and non-PIOG treated patients. Overall, there were no particular groupings of SAEs suggesting any risk of PIOG treatment. Deaths reported during the PIOG studies were slightly lower in PIOG groups than other treatment groups. As attention has focused on cardiovascular safety of PIOG in assessment of Actos over the past few years, a summary of this issue, oedema and weight gain is provided here.

- *Cardiovascular*

Results from short-term placebo-controlled clinical trials showed no evidence of any negative effects on the cardiovascular system with PIOG treatment. Echocardiographic studies show no changes on cardiac structure or function during long-term PIOG therapy. In active and placebo comparator trials with treatment for 1 year, reporting rates of cardiac AEs were similar between PIOG-treated patients and non–PIOG-treated patients. After 2 years of PIOG treatment, more patients receiving PIOG reported cardiac-related AEs compared to patients receiving active comparator (6.3% versus 2.7%). While this data may suggest an increased risk for cardiac-related AEs with long-term PIOG, it is worth noting that more PIOG-treated patients were receiving medications for cardiac therapy at study entry than were gliclazide-treated patients (13.0% versus 9.4%; CTR, page 39 of 68) and that serious cardiac disorders were reported in three patients (approximately 1%) in each treatment group (CTR, Section 12.3.3, page 58 of 68). Furthermore, cardiovascular mortality (as the most objective outcome) was less in PIOG than non–PIOG-treated patients, irrespective of treatment duration. Reporting rates for episodes of heart failure in the placebo and active comparator controlled trials showed no excess in PIOG groups compared to non-PIOG groups. PIOG treatment showed a tendency to reduce blood pressure although changes were only minor. Importantly, however, there was no evidence of any effect of PIOG to increase blood pressure. If some fluid retention does occur with PIOG treatment, it certainly does not result in a secondary effect on blood pressure. In the absence of this, the company considers any negative effects of possible fluid retention on cardiovascular physiology very unlikely.

- *Oedema*

Oedema occurs with PIOG treatment in 6% to 8% of patients treated over 1 year, with slightly higher rates reported over 2 years of treatment (11%). 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 PIOG. In the long-term EC415 study, 1 patient (0.4%, peripheral oedema) receiving PIOG and 1 patient receiving gliclazide (0.3%, oedema NOS) discontinued study drug dosing because of an oedema event. 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.

- *Weight Gain*

After 2 years of treatment in EC415, weight gain was reported as an AE at a slightly higher incidence rate than observed in the short-term monotherapy (7.8% with PIOG and 3.0% with gliclazide in the long-term EC415 study). Consistent with the short-term studies was the relatively low rate of study discontinuation because of weight gain (2.2% with PIOG and 0.3% with gliclazide). Absolute mean weight change increased throughout the PIOG dosing period, reaching a maximum mean (SD) of 4.34 kg (6.11 kg) at Week 104. Among patients receiving gliclazide, mean (SD) weight change peaked at 2.13 kg (5.30 kg) at Week 52; thereafter mean weight change decreased at Week 65 before slowly increasing, reaching a final mean value of 2.06 kg (5.47 kg) at Week 104.

PIO + SU

The combination of PIOG and SU was well tolerated both in short-term studies up to 6 months and in the longer-term study where the incidences of AEs, SAEs, withdrawals due to AEs, and deaths were similar to the combination of SU and MET. Analysis of the most commonly reported AEs showed some variation between different trials, as would be expected. Across all the trials, however, the only AEs which were consistently reported at higher rates with PIOG compared to nonPIOG treatment were oedema and weight increase. These are known effects of PPARγ agonists and are detailed in the SPC.

- *Cardiovascular*

Reporting rates for episodes of heart failure in the placebo and active comparator controlled trials showed no excess in PIOG groups compared to non-PIOG groups. However, in study PNFP-341 there was a small difference in cardiac AE incidence between the two doses of PIOG. This is likely attributed to the higher incidence of congestive heart failure 1.7% vs 0.3%, angina pectoris 0.6% vs 0%, unstable angina 0.3% vs 0%, and palpitations 0.9% vs 0.3%, in the 45 mg PIOG group compared to the 30 mg PIOG group, respectively.

- *Oedema*

The absolute incidence of reports of oedema varies a little between trials. In the 2-year EC409 study, the incidence of oedema for PIOG-treated patients was 10.7% vs. 2.8% for MET-treated patients. Furthermore, there appeared to be a dose-dependent increase in the incidence of oedema in the PNFP-341 study (9.1% in the 30mg dose group vs 13.4% in the 45mg dose group).

- *Weight Gain*

Weight increase was reported as an AE for PIOG when added to SU in 4.4% of patients compared to 0.6% with MET in EC409. After 2 years, in EC409, weight had further increased in PIOG groups, but the rate of weight gain was slower during a second year of treatment. At the end of 2 years, PIOG-treated patients gained on average 3.7 kg in comparison to a mean decrease of 1.7 kg with MET. The incidence of weight gain was slightly higher when PIOG 30 mg was added to SU in study PNFP-010 compared to EC409; this may be a result of the shorter treatment duration in study PNFP-010. Weight gain was noted more often in the PIOG plus SU groups in PNFP-341 compared to either PIOG 30 mg plus SU groups in studies EC409 and PNFP-010, with the highest rates for the PIOG 45 mg plus SU group in PNFP-341. Overall, 5 PIOG-treated patients discontinued study drug dosing because of weight gain recorded as an AE: 4 patients in each treatment group in PNFP-341 and 1 patient in the PIOG plus SU group in EC409.

- *Hypoglycaemia*

Hypoglycaemia was reported at approximately similar rates between treatment groups, suggesting that the addition of PIOG to SU does not pose any greater risk of hypoglycaemia than the addition of MET to SU. Data from the 24-week PNFP-341 suggests that there may be a PIOG dose-dependent effect associated with hypoglycaemia. However, few patients in any PIOG treatment group discontinued from any of the PIOG plus SU combination therapy studies because of hypoglycaemia and the rates for discontinuation for hypoglycaemia were generally similar between treatment groups within studies. For example, in the long-term EC409 study, 1 patient in each treatment group discontinued study drug dosing because of hypoglycaemia over the 2-year treatment period.

In conclusion dose related increases in weight and in peripheral oedema have been seen in the PIOG and SU combination studies. The average weight gain on PIOG plus SU for 2 years was 3.1±4.70kg while patients on MET plus SU lost on average 1.6±4.56kg during the same study. Hypoglycaemia occurred more frequently in the MET/SU group than in the PIOG/SU group in study EC409, 15.6 vs 11.3 %. The PROactive study has been recently published by Dormandy et al and provides further safety data on the use of PIOG as add-on therapy to SU or other hypoglycaemic agents. This was a randomised controlled trial in 5238 patients with T2D and evidence of macrovascular disease where PIO was added to baseline therapy and gradually titrated from 15 to 45 mg daily. The average time of observation was 34.5months. While overall PIOG was associated with a reduction in the composite endpoint of all-cause mortality, non-fatal MI and stroke, there was a significant increased risk of heart failure versus placebo. There was no increased risk of fatal heart failure.

GLIM

In an analysis of pooled data from these trials, the incidence of AEs was similar or lower for GLIM than for the other drugs. In controlled trials in the United States, the most common AEs were dizziness, asthaenia, headache, and nausea, which occurred at the rates of 1.7%, 1.6%, 1.5%, and 1.1%, respectively. A paper by Schneider reviewed treatment-emergent signs and symptoms in 21 placebo- and active-controlled clinical trials of GLIM given for more than 2 weeks in the United States, Europe, and Japan. A total of 6500 patients participated in the trials; more than 4200 received GLIM; and 1500 were treated for more than 1 year. Controlled clinical trials in the United States included 2013 patients who received GLIM; studies in Europe included 1489 patients, and trials in Japan included 718 patients who took GLIM. The most common AEs were upper respiratory infection, headache, accidental injury, flulike syndrome, and sinusitis. Treatment-related signs and symptoms occurred in less than 2% of patients. Dizziness, headache, asthaenia, and nausea occurred in more than 1% of patients. Although hypoglycaemia is more common in patients receiving GLIM than placebo, the incidence of this AE is lower with this second-generation SU than with first-generation drugs in this class. The cumulative incidence of hypoglycaemia summarised in a review paper by McCall was 13.9% in patients receiving GLIM and 2.0% in those taking a placebo. The incidence of hypoglycaemia was 10.0% among patients taking GLIM and 16.3% in those receiving glibenclamide in 1 comparative trial. The cumulative incidence of hypoglycaemia for GLIM was similar to that of glipizide, 21.2% and 20.6%, respectively. Hypoglycaemia indicated by serum glucose levels below 60 mg/dL occurred in 0.9% to 1.7% of patients in two 1-year clinical trials. There is a substantial body of literature on GLIM and the applicant has provided critical review papers on this. It is well-tolerated and hypoglycaemia occurs with a similar or

perhaps lower incidence than with other SUs. The incidence of laboratory-confirmed hypoglycaemia is consistently <1.7% in clinical trial. The risk of cardiovascular events during GLIM treatment was similar to that seen with other SUs. In addition, there is no weight gain and possibly some weight loss associated with its use unlike with some other drugs in this class. Therefore, the choice of GLIM as a SU to combine with PIOG seems justified from a safety perspective.

- Serious adverse event/deaths/other significant events

Deaths reported with PIOG in combination with SU are comparable in number and aetiology with those observed with MET in combination with SU. A slightly higher rate of SAEs was reported for 45 mg compared to 30 mg PIOG when added to SU, and it appears that events related to cardiac function may account for the higher rate seen in the 45 mg group. However, this higher rate may be an artifact of the study design, which stipulated a fixed-dose regimen rather than titration to tolerability. Over treatment periods of up to 2 years, overall discontinuation rates due to AEs with PIOG and SU combination were low and similar to that for MET and SU combination. Gastrointestinal AEs were the most common causes for discontinuation irrespective of treatment group.

- Laboratory findings

Small dose-related decreases in mean haemoglobin and haematocrit levels were observed in short-term studies with PIOG and SU. They were still evident after 2 years of treatment but had not increased. With MET plus SU, mean levels of these variables also decreased but the decreases were slightly less.When added to SU, mean levels of liver enzymes showed a consistent decrease with PIOG treatment, whereas the decreases noted with MET were not consistent and/or smaller than that noted with PIOG. Analyses of changes in individual patients showed no excess of PIOG patients with changes to >3x ULN of liver enzymes compared with MET. LDH and CPK showed increases in mean levels from baseline to end of treatment with PIOG plus SU. Analyses of individual patient changes to >3x ULN and >10x ULN in LDH or CPK in EC409 showed no difference in numbers between PIOG- and MET-treated patients. No negative effects of PIOG on variables reflecting renal function were found. Dose-related decreases in mean haemoglobin and haematocrit levels are known to occur and this is reflected in section 4.4 of the SPC.

- Safety in special populations

There were only small numbers of non-Caucasian patients recruited into the PIOG studies, and no differences in the AE profiles between Caucasian and non-Caucasian subjects were apparent. Considering results from PIOG and nonPIOG treatment groups in the combination therapy studies PNFP-010, PNFP-341, and EC409, no important differences in safety profiles dependent on gender, age, or race were identified. Rates of report of weight increase as an AE appeared to increase with increasing BMI, but other AEs showed no dependency on this variable. No extrinsic factors were found to affect the safety profile of PIOG other than the continent in which trials were performed. In US trials, weight increase was consistently greater than weight changes seen in European trials. This is probably a result of differences in diet, social class of the subjects in the trial, and also dietary advice. In US trials, patients received less dietary advice than in European trials, and as is usual in US studies, a large proportion of the participants were patients without medical insurance. In the opinion of CHMP no SPC comments are needed.

- Safety related to drug-drug interactions and other interactions

A large number of formal pharmacokinetic interaction studies have been undertaken with PIOG, including a SU interaction study, which is described in detail in Section 2.7.2. Although some influence of some drugs on PIOG pharmacokinetic variables were occasionally reported, none was considered clinically relevant, and no warnings concerning dosage adjustments are considered necessary. No relevant pharmacodynamic interactions between PIOG and other drugs were noted in these studies. A large number of concomitant medications were given to patients taking part in the clinical trials. No individual drugs or classes of drugs were identified to have any influence on the reported safety profile, and no interactions were reported.

- Post marketing experience

It is estimated that since the first launch in the US in July 1999 until 31 January 2005, PIOG has been cumulatively prescribed to a total of 5,442,000 patients in the U.S. since launch of the product in July 1999, 724,000 patients in Japan since introduction of the product in December 1999 and 470,000 patients in Europe since introduction of the product in November 2000. This represents an estimated total of 2,929,000 patient years of treatment in the U.S., 962,000 patient years in Japan and 580,000 patient years in Europe. In other areas (Canada, South America, African continent, etc.), where patient exposure is estimated, PIOG has been prescribed to a total of 261,000 patients (487,000 patient years). For the United States, the estimate of

the number of patients being treated with PIOG was obtained from sales data and use of a patient prescription database. In Japan, the estimate of the number of patients being treated with PIOG was obtained using a patient prescription database and patient years were calculated with the quantity of tablets shipped. In Europe, patient exposure was estimated from data on the number of prescriptions written and/or packs sold and distributed as samples (different methods being used in different countries). The use of PIOG as monotherapy and with different combinations was estimated based on data from a prescription database in the United States and the postmarketing investigation database in Japan. In the United States, the most frequent use appeared to be as monotherapy. In Japan, PIOG was most often prescribed in combination with SUs. PIOG is not indicated in Japan for use with MET or insulin. The following sections firstly summarise the post-marketing data as presented in the ISS in 2002 and then the cumulatively reported events up to 31 January 2005 as presented in the 6th to 11th Periodic Safety Update Report (PSUR). The full extensive reports are included in Module 5 of this submission. Case narratives of all deaths are appended to this section, other non-fatal case narratives are located in the individual PSURs and the ISS. 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 PIOG regarding malignancy has been compiled and submitted to Regulatory Agencies for approval. The company has also agreed with regulators a series of preclinical studies to further investigate mechanisms of bladder cancer seen in male rats in long-term carcinogenicity studies. In addition, a pharmacovigilance plan consisting of both clinical studies and epidemiological studies to assess effects of PIOG on incidence of bladder cancer in humans has also been initiated. There is an accumulating literature (mainly from animal studies) to suggest that PPAR agonists as a class have effects on development of neoplasia in a number of tissues, however an exact role has not yet been defined. Although it is the position of the company that the weight of evidence currently suggests a protective role, at the request of regulators the pharmacovigilance plan has been revised now also to include a series of studies designed to identify and then to clarify any signals of effects of PIOG on incidence of malignancies other than bladder cancer.

PIOG and SU Combination Therapy
As outlined above, on the market, about 31% and up to 66% of PIOG therapy is in free combination with a SU in the US and Japan, respectively, 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. From the adverse event profiles of SUs, it could be expected to see a higher incidence of hypoglycaemia when PIOG is added to the therapy; however, in the clinical trials as described in this ISS and from the spontaneous reports from the market, the combination therapy appears not to yield a shift of the ADR profile. There is currently no marketing authorisation for the fixed combination product and thus no postmarketing experience available yet.

Review of postmarketing data from the use of PIOG, as monotherapy or in free combination with SU, has not resulted in any new safety concern other than those listed or under ongoing review for PIOG. Specific data on use of PIOG with GLIM has not been provided and this is considered acceptable.

- Discussion on clinical safety

The assessment of the safety of PIOG/GLIM relies on the more recent clinical studies conducted to support the authorisation of PIOG and to amend the product information since 1999, literature review of the clinical safety of GLIM and post-marketing safety data from use of PIOG. Limited safety data is also available from the four phase 1 studies conducted with the FDC. In the phase 1 program, 133 healthy adults each received at least one dose of one of the three combination products. There were no clinically surprising events across these 4 studies – most events being mild in intensity, resolving without the need for treatment - dizziness and headache being the most frequent and of similar incidence between the combination products and the commercially available individual tablets. For what its worth there were no deaths, SAEs or other unusual occurrences amongst these volunteers and similarly there were no clinically meaningful treatment-related effects on temperature, blood pressure, pulse, laboratory tests or ECGs, nor were there any abnormal findings on physical examination. There is a substantial body of literature on GLIM and the applicant has provided critical review papers on this. It is well-tolerated and hypoglycaemia occurs with a similar or perhaps lower incidence than with other SUs. The incidence of laboratory-confirmed hypoglycaemia is consistently <1.7% in clinical trial. The risk of cardiovascular events during GLIM treatment was similar to that seen with other SUs. In addition, there is no weight gain and possibly some weight loss associated with its use unlike with some other drugs in this class. Therefore, the choice of GLIM as a SU to combine with PIOG seems justified from a safety perspective.

The combination of PIOG and SU was well-tolerated both in short-term studies up to 6 months and in the long-term study of 104 weeks' duration, where the incidence of AEs, SAE, withdrawals due to AEs and deaths was similar to the combination of SU and MET. Weight gain and oedema occurred with a similar frequency to that seen with PIOG monotherapy. Hypoglycaemia was seen more frequently with the MET and SU combination that with PIOG and SU. Nevertheless, there is a potential for increased risk of hypoglycaemia with the FDC as the minimum dose of PIOG is 30mg. In order to minimise this risk, it should be clearly stated in the SPC that patients should be titrated with the individual components before switching to the FDC.
Postmarketing data do not indicate any new safety concerns for PIOG in free combination with SU.
While there is no safety data with the FDC in diabetic subjects, this is justified on the basis that the safety of PIOG and SU in combination is established. Further reassurance on the safety of PIOG and GLIM at maximum dose was requested with specific data to be presented from the three PIOG/SU studies. This has been provided and no new concerns arise.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the detailed description of the PhV system should be supplemented with additional required information in particular on the organisational aspects, procedures and database as per the *Draft Guideline on monitoring of compliance with pharmacovigilance regulatory obligations on pharmacoviginance inspections.* The applicant committed to provide the supplementary information as part of follow-up measures.

Risk Management Plan

The MAA submitted a risk management plan

The MAA submitted a risk management plan in accordance with Guideline EMEA/CHMP/96268/2005. This addressed the known safety profile of PIOG and GLIM and the safety aspects of the combined use of PIOG and SUs. There is very limited data on the use of the 2 components concomitantly or the FDC. The issues in relation to PIOG have previously been assessed. The following is a summary of the RMP.

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 (01-00-TL-OPI-506) in PIOG 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. Resultsfrom PROactive study 3. Analysis from ongoing clinical trials 4. PIOG 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. PIOG clinical trial to investigate mechanisms	Section 4.4 and 4.8 of the SmPC and the Package Leaflet to be updated to reflect finding (pending review in progress).
Hypersensitisation,	1. Routine pharmacovigilance including review in PSURs	Contraindication in section 4.3 of the SPC for hypersensitivity to GLIM or other SU Hypersensitivity reactions described in section 4.8
Blood dyscrasias,	1. Routine pharmacovigilance including review in PSURs	Precautions and recommendations for regular haematological monitoring in section 4.4 and 4.8 of the SPC.
Hypoglycaemia	1. Routine pharmacovigilance including review in PSURs	Precautions and recommendations for monitoring in section 4.4 and 4.8 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. At the time of the CHMP opinion, there were a number of minor unresolved quality issues without impact on the clinical efficacy or safety of the product, therefore the applicant made a commitment to resolve these as post-opinion follow-up measures.

Non-clinical pharmacology and toxicology
No new non-clinical studies were conducted with the fixed formulation compound. In view of the length and extent of clinical experience obtained with co-administration of commercially available PIOG and GLIM, the CHMP considered the absence of animal studies cited under indents 4.2.1 to 4.2.3 (a to f) inclusive of Annex I to Directive 2001/83/EC, as amended, justified. The carcinogenic potential of PPAR agonists in general is of significant concern to regulators. Both PIOG and GLIM display PPARγ agonist activity. Due to the high protein binding of both PIOG (>98%) and GLIM (>99% in all species tested and >99.5% in humans) the applicant committed to evaluate the potential of the individual compounds to influence the individual free fractions and in the presence of such an interaction between PIOG and GLIM on the protein binding profile, to recalculate of the safety margins in relation to carcinogenic potential for both GLIM and PIOG based on plasma concentrations (AUCs) of the free fraction in relation to the proposed dosage regimens. The data related to these concerns will be provided as part of the follow up measures.

Efficacy
This application was for a fixed dose combination, containing two authorized ingredients, pioglitazone hydrochloride and glimepiride in two strengths: 30mg/4mg and 45mg/4mg tablets (initially for three strengths including also 30mg/2mg but this strength was withdrawn from the application by MAH). Four clinical pharmacology studies were submitted with this application. These bioequivalence studies were completed to demonstrate that 3 initially proposed doses of the FDC are bioequivalent to the concomitantly administered individual tablets. Bioequivalence of the 30 mg/4 mg and 45 mg/4 mg doses were proven. However the applicant failed to demonstrate the bioequivalence of the 30mg/2mg tablet and withdrawn it from the application. The bioequivalence studies served to bridge the clinical safety and efficacy data for PIOG and GLIM to the FDC tablet. No efficacy studies have been conducted with the FDC. The indications for Tandemact were modified to reflect the need to titrate patients with optimal doses of individual components of the combination before switching to FDC. No scientific advice has been given in relation to this application.

Safety
The concomitant usage of PIOG and SU agents, both in the submitted phase III programme and subsequently to granting of the marketing authorisation appears to be well tolerated and has not led to any unexpected adverse events. The safety profile for GLIM is generally similar to the other SUs, so it is argued that this specific PIOG / GLIM combination should not prove significantly different from that observed when co-prescribed with other SUs. It is stated that PIOG is taken concomitantly with a SU in 31% of appropriately treated diabetic patients in the USA and 66% in Japan. The SPC for the fixed combination accommodates the advice and warnings required from both PIOG and GLIM licenses.

- User consultation

The applicant committed to perform user testing and to provide the results not later then two months after the granting of the Marketing Authorisation, as addressed in the follow-up measures.

Risk-benefit assessment

The CHMP, having considered the data submitted on quality, safety and efficacy was of the opinion that the risk-benefit balance is positive for two of the three strengths of Tandemact initially submitted. The applicant failed to demonstrate the bioequivalence of the 30mg/2mg tablet and withdrawn it from the application. Also the indications for Tandemact were modified to reflect the need to titrate patients with optimal strengths of individual components of the combination before switching to FDC.

A risk management plan was submitted and was considered appropriate. The CHMP, having considered the data submitted was of the opinion that routine the pharmacovigilance was adequate to monitor the safety of the product and no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority that the risk-benefit balance of Tandemact in the treatment of patients with type 2 diabetes mellitus who show intolerance to metformin or for whom metformin is contraindicated and who are already treated with a combination of pioglitazone and glimepiride was favourable and therefore recommended the granting of the marketing authorisation.