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Pioglitazone/Metformin

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Contents

Abstract

▲ A fixed-dose pioglitazone/metformin tablet is approved in the US and the EU for the treatment of adult patients with type 2 diabetes mellitus who currently have inadequate glycaemic control with metformin monotherapy. In the US, the combination tablet is also approved for the treatment of adult patients with type 2 diabetes who currently have inadequate glycaemic control with pioglitazone monotherapy and for those already receiving a combination of pioglitazone and metformin.

▲ Bioequivalence, based on absorption and bioavailability parameters, has been established between the fixed-dose tablets and equivalent doses of pioglitazone and metformin coadministered as separate agents.

▲ Combination therapy with pioglitazone plus metformin was significantly more effective at improving both glycaemic and lipid control than metformin plus placebo in patients with type 2 diabetes in a 16-week, well designed trial.

▲ Pioglitazone plus metformin demonstrated similar antihyperglycaemic efficacy to that of rosiglitazone plus metformin in a well designed 12-month trial; however, pioglitazone plus metformin was the superior combination in terms of lipid control.

▲ In several comparative trials of 1–3.5 years' duration, pioglitazone plus metformin was at least as effective as combination therapy with a sulphonylurea plus metformin in terms of antihyperglycaemic efficacy, but provided superior lipidaemic control with regard to levels of triglyceride and high-density lipoprotein-cholesterol.

▲ Pioglitazone plus metformin was generally well tolerated in patients with type 2 diabetes, with adverse events common to metformin monotherapy observed at a similar incidence to that with metformin plus placebo.

Features and properties of pioglitazone/metformin (ACTOplus met™; Competact™)	
Indications	
Type 2 diabetes mellitus inadequately controlled with pioglitazone (PIO) or metformin (MET) monotherapy or adequately controlled with a combination of PIO and MET **(US)**; Type 2 diabetes mellitus inadequately controlled with MET monotherapy **(EU)**	
Mechanism of action	
PIO: Primarily decreases insulin resistance	
MET: Primarily reduces hepatic gluconeogenesis	
ACTOplus met™ dosage and administration (US)[a]	
Inadequately controlled glycaemia with PIO alone or MET alone	15mg/500mg or 15mg/850mg once or twice daily
Currently receiving PIO plus MET	15mg/500mg or 15mg/850mg once or twice daily
Maximum recommended dosage	45mg/2550mg daily
Route of administration	Oral
Proposed Competact™ dosage and administration (EU)[a]	
Inadequately controlled glycaemia with MET alone	15mg/850mg twice daily
Route of administration	Oral
Adverse events occurring in ≥5% of patients (treated with pioglitazone plus metformin) with an incidence >2% that of MET monotherapy recipients	
Oedema and headache	
[a] Local prescribing information should be consulted for further details regarding PIO/MET dosage regimens	

Diabetes mellitus, a chronic metabolic disorder of carbohydrate metabolism, is responsible for the deaths of 3.2 million people worldwide every year.[1] Approximately 5% of the world's adult population was estimated to have diabetes in 2005, with an estimated increase to >6% by 2025.[2]

Type 2 diabetes accounts for up to 95% of the diabetes cases diagnosed in developed countries, and is now one of the leading contemporary causes of premature death and morbidity.[2,3] Characterised by hyperglycaemia, due to insulin resistance and relative insulin deficiency,[3,4] type 2 diabetes may develop owing to any number of risk factors including increasing age, low physical activity and obesity,[3] the primary risk factor.[2]

Chronic hyperglycaemia, along with other contributory factors such as abnormal lipid levels, affects numerous organ systems and leads to complications such as retinopathy, nephropathy, neuropathy and coronary heart disease.[2] Cardiovascular disease is the leading cause of death in patients with type 2 diabetes because of the collection of cardiovascular risk factors in this patient population, which includes dyslipidaemia, hyperinsulinaemia, hypertension, glucose intolerance and central obesity.[2]

Elevated blood glucose levels can often be initially controlled by lifestyle modifications such as improved diet and exercise, which help to reduce weight and consequently insulin resistance.[3,5] However, the sequential addition of one or more pharmacological agents is often required to maintain glycaemic control.[5] Combining agents with differing mechanisms of action may provide additive/synergistic clinical benefits.[6-8]

One such combination regimen is pioglitazone plus metformin. Pioglitazone is an insulin-sensitising antihyperglycaemic agent of the thiazolidinedione class, and improves glycaemic control primarily by increasing peripheral glucose utilisation.[9] Metformin, a member of the biguanide class of antihyperglycaemic agents, reduces plasma glucose levels principally by decreasing endogenous hepatic gluconeogenesis.[9] Moreover, both pioglitazone and metformin monotherapies are associated with an improvement in the cardiovascular outcome of patients with type 2 diabetes, according to the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study[10] and the UKPDS (UK Prospective Diabetes Study),[11] respectively. Both pioglitazone and metformin can be used as monotherapy[5,12] and with differing mechanisms of action, the two agents may also be used concomitantly to further improve glycaemic control.[5]

However, multi-drug regimens are associated with poorer patient compliance than monotherapies.[13] The availability of pioglitazone and metformin as a fixed-dose combination tablet (ACTOplus met™ [15mg/500mg and 15mg/850mg]; Competact™ [15mg/850mg])[1] increases the convenience of administration for the patient and as such, may improve patient compliance.

This article reviews the pharmacological properties and clinical use of coadministered pioglitazone and metformin in patients with type 2 diabetes.

1. Pharmacodynamic Profile

The pharmacodynamic activities of pioglitazone and metformin given as individual agents in patients with type 2 diabetes are well established and have been extensively reviewed elsewhere.[14-16] Therefore, this section focuses on the pharmacodynamic effects of the coadministered agents. Further results from some clinical trials[8,17-23] are presented in section 3. Some of the data are available only as abstracts and/or posters.[21,24-28]

- The thiazolidinedione pioglitazone is a potent, high-affinity agonist for peroxisome proliferator-activated receptor-gamma (PPARγ).[14] PPARγ is a ligand-activated transcription factor that regulates the expression of insulin-responsive genes involved in the modulation of glucose and lipid metabolism.[14]
- In patients with type 2 diabetes, pioglitazone reduces hyperglycaemia and hyperinsulinaemia by reducing insulin resistance in the periphery, liver

1 The use of trade names is for product identification purposes only and does not imply endorsement.

and adipose tissue, thus facilitating insulin-dependent glucose disposal and decreasing the demand for insulin production and hepatic glucose output.[9,14]

- Pioglitazone may also improve β-cell function in this patient population, by β-cell PPARγ activation and/or by reducing lipotoxicity and the need for insulin production.[14] However, pioglitazone treatment is associated with an increase in whole body adiposity, owing to the promotion of lipid storage and subcutaneous redistribution of the visceral adipose tissue deposits which often accumulate to excess in patients with insulin resistance.[14]
- The antihyperglycaemic effect of the active metabolites of pioglitazone (MII, MIII and MIV) is ≈40–60% that of pioglitazone according to animal studies.[14]
- Metformin is a biguanide that lowers fasting and postprandial plasma glucose levels primarily by reducing elevated rates of hepatic gluconeogenesis in patients with type 2 diabetes, and also by reducing intestinal glucose absorption.[9,16] Glucose disposal in peripheral tissues may also be increased with metformin, resulting in improved insulin sensitivity.[9,16] Metformin may also protect β-cells from the deleterious effects of lipotoxicity by reducing free fatty acid levels, thus improving β-cell function.[29]

Effects on Insulin

- Insulin resistance was reduced with pioglitazone plus metformin in patients with type 2 diabetes naive to treatment,[27] with inadequate glycaemic control with metformin[8,17,23] or experiencing adverse events with the maximum tolerated dose of metformin.[23] For example, in a 16-week trial, insulin resistance was significantly reduced from baseline with the addition of pioglitazone 30mg once daily to metformin therapy (n = 168) and significantly increased with the addition of placebo (−16.2% vs +17.6%; $p \leq 0.05$ for both comparisons vs baseline and the between-group comparison) [n = 160], according to Homeostasis Model Assessment (HOMA) insulin resistance estimates.[8]
- Additional data[17] from this study[8] confirmed significantly greater increases from baseline in insulin sensitivity in the pioglitazone plus metformin than placebo plus metformin group, using both HOMA-Insulin Sensitivity (HOMA-S) [+16% vs 0%; $p = 0.002$; n = 157 and 147, respectively] and the Quick Insulin Sensitivity Check Index (QUICKI) [+0.014 vs 0.000 units; $p = 0.0001$; n = 157 and 148] analyses. Reductions in the pioglitazone plus metformin group were also significant versus baseline values for HOMA-S and QUICKI (both $p \leq 0.0001$).[17]
- Pioglitazone treatment was superior to that of gliclazide, when added to metformin therapy, in terms of improving insulin sensitivity, in patients with type 2 diabetes who achieved insufficient glycaemic control with metformin alone.[20] After 52 weeks of treatment, insulin sensitivity was significantly increased from baseline with pioglitazone plus metformin compared with gliclazide plus metformin, according to composite insulin sensitivity index analyses ($p < 0.0001$).[20]
- More effective, long-term improvements in insulin sensitivity were achieved with pioglitazone treatment than with glibenclamide, when added to a stable metformin regimen.[21] Insulin sensitivity was initially increased from baseline by 42% ($p < 0.001$) with pioglitazone plus metformin and by 10% with glibenclamide plus metformin. However, only pioglitazone plus metformin recipients experienced sustained improvements in insulin sensitivity throughout the 3.5-year study, whereas there was a gradual decrease from baseline in insulin sensitivity of 32% in the glibenclamide plus metformin group. The between-group difference was significant from 6 months onwards (all $p < 0.005$).[21]
- As add-on therapy to metformin, pioglitazone may reduce the demand for insulin production and thus improve or stabilise β-cell function compared with the addition of a sulphonylurea[18,19,21,22,25] and metformin monotherapy[23,24,27] in patients with type 2 diabetes.

Effects on Cardiovascular Risk Factors

- Pioglitazone reduces cardiovascular risk factors associated with type 2 diabetes, including dyslipidaemia, has antiatherogenic and antihypertensive effects and reduces microalbuminuria, an indi-

cator of renal and cardiovascular damage.[14] Metformin also improves cardiovascular risk factors in this patient population, including improvements in lipid profiles and endothelial function, and reductions in C-reactive protein levels, plasminogen activator inhibitor-1 activity and bodyweight.[15,16]

- The beneficial effects on cardiovascular risk factors observed with pioglitazone and metformin monotherapies are supported by results of studies of their use as combination therapy in patients with type 2 diabetes.[18,19,23,26,28] For example, in a 16-week double-blind trial in patients (n = 301) with inadequately controlled type 2 diabetes despite metformin treatment, the mean atherogenic index of plasma (AIP) was reduced from baseline by a significantly greater extent with add-on pioglitazone 30mg daily plus metformin than with add-on placebo (−0.09 vs 0.00; p = 0.0001) [baseline values 0.37 and 0.36].[28] AIP is inversely correlated with low-density lipoprotein-cholesterol (LDL-C) particle size.

- Furthermore, pioglitazone plus metformin combination therapy was superior to that of a sulphonylurea agent plus metformin in these studies in terms of improving cardiovascular risk factors.[18,19,26] For example, in a double-blind trial in patients (n = 330) with inadequate glycaemic control with metformin alone, a significantly greater decrease from baseline in the AIP value was exhibited in recipients of pioglitazone plus metformin therapy compared with gliclazide plus metformin recipients after 52 (0.36 vs 0.06; p = 0.001)[18] and 104 (0.46 vs 0.14; p < 0.001) weeks of treatment.[19]

- Pioglitazone plus metformin treatment was at least as effective as rosiglitazone plus metformin in terms of improvements in non-conventional cardiovascular risk parameters.[23] In a 12-month double-blind trial in patients with metabolic syndrome and type 2 diabetes (n = 96) who had inadequate glycaemic control or were experiencing adverse events with metformin, mean levels of lipoprotein (a) [a marker of atherosclerosis and coronary heart disease] were significantly (p < 0.05) reduced from baseline with pioglitazone plus metformin and to a greater extent than with rosiglitazone plus metformin (0.06 vs 0.01 mmol/L; p < 0.05) at end of trial. Mean baseline values were 0.44 and 0.45 mmol/L respectively. However, the change from baseline (0.0109 vs 0.0104 mmol/L) in mean homocysteine levels (a risk factor for atherogenic events) was significant for both pioglitazone plus metformin (−0.0023 mmol/L; p < 0.05) and rosiglitazone plus metformin therapy (−0.0024 mmol/L; p < 0.05) at the end of the trial.[23]

- Pioglitazone as an add-on therapy to metformin was significantly more effective at reducing microalbuminuria, a classic cardiovascular risk marker, than the addition of gliclazide.[18] The mean urinary albumin/creatinine ratio decreased from baseline in the pioglitazone group by 10% versus a 6% increase in the gliclazide group after 52 weeks of treatment (p = 0.027).[18]

2. Pharmacokinetic Profile

This section focuses on the pharmacokinetic parameters of pioglitazone and metformin when administered as a fixed-dose combination, and is supplemented with data on pioglitazone and metformin administered as separate agents, previously reviewed elsewhere.[14-16,30]

Bioequivalence, based on absorption and bioavailability parameters, with respect to both pioglitazone and metformin, has been established for each of the recommended fixed-dose combination tablets (pioglitazone/metformin 15mg/500mg and 15mg/850mg) and the correlating dosages of pioglitazone and metformin administered as separate agents in healthy volunteers under fasting conditions.[9]

Data were obtained from the US manufacturer's prescribing information,[9] from an absorption study in healthy volunteers[31] and comprehensive reviews of pioglitazone.[14,30]

Absorption and Distribution

- Following a single fixed dose of pioglitazone/metformin 15mg/500mg, the mean maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from time zero to infinity

(AUC_∞) and the time taken to reach C_{max} (t_{max}) values were 585 ng/mL, 5984 ng • h/mL and 1.83 hours, respectively, for pioglitazone in healthy volunteers under fasting conditions. The equivalent C_{max}, AUC_∞ and t_{max} values of metformin were 1203 ng/mL, 7783 ng • h/mL and 2.32 hours.[9]

- In the same study, after a single fixed dose of pioglitazone/metformin 15mg/850mg, mean C_{max}, AUC_∞ and t_{max} values for pioglitazone were 569 ng/mL, 5671 ng • h/mL and 1.89 hours; corresponding values for metformin were 1827 ng/mL, 11 927 ng • h/mL and 2.41 hours.[9]
- Pioglitazone absorption was slightly delayed by food, although systemic exposure was not affected.[30] However, the extent and rate of absorption of a single oral dose of metformin 850mg was reduced with food intake in healthy volunteers; mean C_{max} and AUC values were reduced by 39% and 24%, and t_{max} was 37 minutes longer in the fed versus the fasting state.[31] The clinical relevance of these results is unknown.[9]
- The mean absolute bioavailability of pioglitazone following administration of oral pioglitazone 7.5mg in healthy volunteers was 83%.[30] The absolute bioavailability of a single oral dose of metformin 500mg is ≈50-60% under fasting conditions[9] and is 14% higher than that of an 850mg dose.[31]
- Pioglitazone and its active metabolites, M-III and M-IV, are >99% and >98% plasma protein bound, predominantly to serum albumin.[9] Pioglitazone has a mean apparent volume of distribution of 0.63 L/kg following a single dose.[9]
- Metformin is negligibly plasma protein bound, although it does partition into erythrocytes and has an average apparent volume of distribution of 654L following single oral doses of 850mg.[9]

Metabolism and Elimination

- Pioglitazone undergoes extensive metabolism, via oxidation and hydroxylation, to active metabolites including M-II, M-IV and M-III.[9] Metabolism of pioglitazone occurs primarily via the cytochrome P450 (CYP) enzymes CYP2C8/9 and CYP3A4, according to *in vitro* studies.[30] At steady state, pioglitazone accounts for 20–25% of the total exposure in healthy volunteers and patients with type 2 diabetes.[9]
- After oral administration of pioglitazone, approximately 15–30% of the dose is recovered in the urine, with the majority presumed to be eliminated via faeces as either unchanged parent drug or its metabolites.[9] The apparent clearance of pioglitazone is 5–7 L/h.[9] The mean terminal elimination half-life ($t_{1/2}$) of pioglitazone and pioglitazone inclusive of its metabolites is 3–7 hours and 16–24 hours, respectively.[9]
- Following a single fixed dose of pioglitazone/metformin 15mg/500mg in healthy volunteers, the $t_{1/2}$ of pioglitazone was 8.69 hours; the corresponding value after a single fixed dose of pioglitazone/metformin 15mg/850mg was 7.19 hours.[9]
- Metformin is not metabolised hepatically and is excreted unchanged in the urine following a single intravenous dose in healthy volunteers.[9] Elimination of ≈90% of an oral metformin dose occurs within the first 24 hours via the kidneys, primarily by tubular secretion, with a plasma $t_{1/2}$ of ≈6.2 hours. The blood $t_{1/2}$ of metformin is 17.6 hours, because of the distribution of metformin in erythrocytes.[9]
- The $t_{1/2}$ of metformin was 8.57 hours following a single fixed dose of pioglitazone/metformin 15mg/500mg combination in healthy volunteers; the corresponding value after a single fixed dose of pioglitazone/metformin 15mg/850mg was 17.56 hours.[9]

Special Patient Groups

- The pharmacokinetic profile of pioglitazone does not differ to any clinically significant degree in elderly or adolescent patients.[14] No differences considered clinically relevant have been observed in the pharmacokinetic profile of metformin in healthy elderly volunteers.[9] There are also no clinically relevant effects of sex on the pharmacokinetic profiles of pioglitazone and metformin.[9]
- The renal clearance of metformin is reduced in patients with renal impairment in proportion with creatine clearance.[9] Consequently, metformin plasma and blood $t_{1/2}$ values are increased in this patient

population. Metformin, and thus pioglitazone/metformin, is contraindicated in patients with renal impairment.[9]

- The mean C_{max} of pioglitazone was 43% less and the volume of distribution was 55% greater in 12 patients with chronic hepatic impairment (Child-Pugh B or C) than in 12 healthy volunteers following a single oral dose of pioglitazone 30mg,[30] although the mean AUC and total clearance were similar between groups.[30] Treatment with pioglitazone/metformin should not be initiated in patients with hepatic impairment.[9]

Drug Interactions

- As may be predicted from the extensive metabolism of pioglitazone by the CYP enzymes CYP2C8/9 and CYP3A4, coadministration of CYP2C8/9 and CYP3A4 inhibitors, such as gemfibrozil[32] and ketoconazole,[9] may increase pioglitazone exposure. In contrast, pioglitazone exposure may be reduced upon coadministration of CYP enzyme inducers such as rifampicin, which reduces the plasma concentration of pioglitazone most probably via CYP2C8 induction.[33]

- Changes in the pharmacokinetic profiles of pioglitazone and drugs including nifedipine, atorvastatin calcium, ethinyl estradiol and midazolam, have been reported upon coadministration.[9] Local prescribing information should be consulted for further information.[9]

- The pharmacokinetic profiles of glipizide, fexofenadine, digoxin, warfarin, theophylline and ranitidine HCl were not significantly affected by pioglitazone in drug interaction studies.[9]

- Drug interactions with metformin have been reported for nifedipine and furosemide.[9] Metformin may interact with cationic drugs that are eliminated via renal tubular secretion, such as cimetidine and vancomycin, as common tubular transport systems may be competed for during excretion.[9] Local prescribing information should be consulted for further information.[9]

3. Therapeutic Efficacy

The efficacy of pioglitazone plus metformin combination therapy has been evaluated in adult patients with inadequately controlled type 2 diabetes despite treatment with metformin and/or other oral antihyperglycaemic agents in several randomised, placebo- or active comparator-controlled trials of up to 3.5 years duration.[8,18,19,21-23,34,35]

These data are supported by a large (n = 827), randomised, 24-week trial in the same patient population; reported in the manufacturer's prescribing information.[9] In this trial, the addition of pioglitazone 30 or 45mg once daily to metformin improved glycaemic control relative to baseline, irrespective of the pioglitazone dosage.[9]

Clinical trials evaluating the efficacy of the fixed-dose combination tablet have not been performed; as such, all clinical trials discussed in this section assess the efficacy of pioglitazone and metformin coadministered as separate agents.

Versus Placebo plus Metformin

In the pivotal, well designed 16-week trial, 328 patients received single-blind placebo for 1 week or 4 weeks in addition to their usual metformin monotherapy or combination regimen, respectively, in a 6-week pre-trial washout period during which antidiabetic medication other than metformin was discontinued.[8] Patients with glycosylated haemoglobin (HbA_{1c}) ≥8.0% following the single-blind period were randomised to receive double-blind pioglitazone 30mg plus metformin (n = 168) or placebo plus metformin (n = 160) once daily. Patients who completed the 16-week, double-blind phase were eligible to receive open-label pioglitazone 30mg once daily in combination with their usual metformin dosage for a duration of 72 weeks. The pioglitazone dosage was increased to 45mg once daily only in patients who exhibited unacceptable glycaemic control.[8]

Eligibility criteria included a stable metformin regimen for ≥30 days and a fasting C-peptide value >1.0 ng/mL.[8] Patients receiving lipid-lowering medications were eligible if a stable regimen had

been maintained for >60 days. Patient exclusion criteria included unstable cardiovascular and cerebrovascular conditions within the prior 6 months and/or rapidly progressive or unstable nephropathy, retinopathy or neuropathy.[8]

There were no between-group differences in baseline characteristics, with patients having a mean age of ≈55 years, a mean HbA_{1c} of ≈9.8% and a mean fasting plasma glucose (FPG) level of ≈14 mmol/L. Seventy percent of patients were receiving metformin monotherapy and 30% were being treated with antidiabetic medications in addition to metformin, commonly glibenclamide (glyburide) and glipizide.[8]

Glycaemic control was evaluated by changes in HbA_{1c} and FPG.[8] Efficacy with regard to lipid control was assessed by changes in levels of high-density lipoprotein-cholesterol (HDL-C), LDL-C and triglycerides. Whether endpoints were primary or secondary was not specifically identified. Analyses used the intent-to-treat (ITT) population using a last-observation-carried-forward method.[8]

- Combination therapy with pioglitazone 30mg plus metformin significantly improved glycaemic control in patients with type 2 diabetes inadequately controlled with metformin alone.[8] Least squares mean HbA_{1c} was significantly reduced from baseline at all timepoints from 4 weeks onwards in pioglitazone plus metformin recipients compared with significant increases in the placebo plus metformin group (all $p \leq 0.05$). At study end, the between-group difference of −0.83% was significant (figure 1).

- Pioglitazone plus metformin was also more effective at reducing FPG levels than metformin alone (figure 1).[8] Least squares mean FPG levels were significantly (all $p \leq 0.05$) reduced from baseline from 4 weeks onward with pioglitazone plus metformin but not with placebo plus metformin, with a significant ($p \leq 0.05$) difference between treatment groups of −2.09 mmol/L at 16 weeks (figure 1).[8]

- Furthermore, the beneficial effects of pioglitazone plus metformin treatment on glycaemic control were sustained during the open-label extension

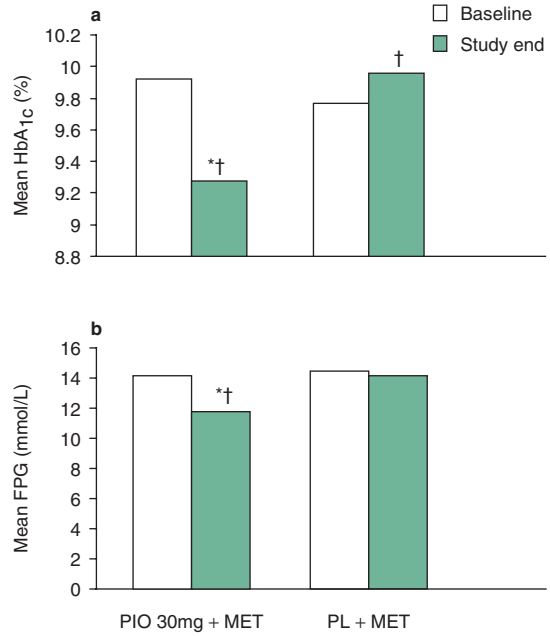

Fig. 1. Efficacy of oral pioglitazone (PIO) plus metformin (MET) in type 2 diabetes mellitus. Levels of (**a**) glycosylated haemoglobin (HbA_{1c}) and (**b**) fasting plasma glucose (FPG) at baseline and end of trial in patients with type 2 diabetes with inadequate glycaemic control despite MET monotherapy in a randomised, double-blind, 16-week trial.[8,9] Patients received PIO 30mg plus MET (n = 168) or placebo (PL) plus MET (n = 160), once daily; MET dosages were equal to individual pre-trial regimens. * $p \leq 0.05$ vs PL + MET; † $p \leq 0.05$ vs baseline.

phase.[8] After 72 weeks of treatment, patients (n = 154) exhibited least squares mean changes from baseline in HbA_{1c} and FPG of −1.36% and −3.5 mmol/L.

- Lipid profiles in patients with inadequately controlled type 2 diabetes despite metformin monotherapy improved with add-on pioglitazone therapy.[8] Least squares mean triglyceride levels were reduced significantly ($p \leq 0.05$) from baseline by 9.7% with pioglitazone plus metformin compared with an increase of 8.5% with placebo plus metformin. Respective least squares mean baseline triglyceride levels were 3.37 and 3.39 mmol/L.[8] At study end, the between-group difference was significant ($p \leq 0.05$).[8]

- Least squares mean changes in levels of HDL-C were increased significantly ($p \leq 0.05$) in pioglitazone plus metformin but not placebo plus

metformin recipients (10.2% vs 1.5%; $p \leq 0.05$) from least squares mean baseline levels of 1.11 and 1.09 mmol/L. Least squares mean changes from baseline in LDL-C (0.2 vs 0.31 mmol/L) and total cholesterol (0.11 vs 0.03 mmol/L) levels were not significantly different between pioglitazone and placebo treatment groups. Respective mean baseline LDL-C levels were 3.09 and 3.05 mmol/L; corresponding total cholesterol levels were 5.50 and 5.48 mmol/L. The increases from baseline in these lipid parameters were significant (both $p \leq 0.05$) in recipients of pioglitazone plus metformin.[8]

Versus a Thiazolidinedione plus Metformin

The clinical efficacy of pioglitazone plus metformin combination therapy has been compared with that of rosiglitazone plus metformin in 96 patients with type 2 diabetes in addition to metabolic syndrome in a randomised, double-blind, multicentre, 1-year trial.[23]

Eligibility criteria included a type 2 diabetes duration of ≥6 months and inadequate glycaemic control (HbA_{1c} >7.5%) with, or poor tolerability to diet and metformin therapy at the maximum tolerated dose. All patients had metabolic syndrome, hypertension, a body mass index of 25.0–28.1 kg/m^2, triglyceride levels of ≥1.69 mmol/L and fasting C-peptide levels of >1.0 ng/mL.[23] Exclusion criteria included those covered in local prescribing information and the presence of severe anaemia or unstable or rapidly progressive diabetic neuropathy, nephropathy or retinopathy. Baseline patient characteristics included a mean age of ≈55.5 years, a mean HbA_{1c} of ≈8.15% and mean FPG and postprandial plasma glucose (PPG) levels of ≈9.02 and ≈10.66 mmol/L.[23]

Patients received oral pioglitazone 15mg once daily (n = 48) or rosiglitazone 4mg once daily (n = 48), before a midday meal, in addition to metformin 1500 mg/day.[23] Metformin dosages were subsequently titrated to a maximum of 3000 mg/day according to efficacy and tolerability.

Primary efficacy evaluations included changes in levels of HbA_{1c} and lipids (HDL-C, LDL-C, total cholesterol and triglycerides); primary endpoint assessments were made after 52 weeks of treatment. Other efficacy parameters included changes in FPG and PPG levels. Analyses used the ITT population.

- Pioglitazone plus metformin combination therapy showed similar efficacy, in terms of glycaemic control, to that of rosiglitazone plus metformin in patients with type 2 diabetes and metabolic syndrome.[23] Significant reductions from baseline (8.2% vs 8.1%) in HbA_{1c} were observed in both pioglitazone plus metformin and rosiglitazone plus metformin treatment groups at the end of the 52-week trial (1.4% and 1.3%; both $p < 0.01$ vs baseline) [primary endpoint], with recipients of both treatments exhibiting significant reductions from baseline after 9 months of treatment (1.2% and 0.7%; both $p < 0.05$ vs baseline).[23]

- Furthermore, reductions in mean levels of FPG and PPG were similar in both treatment groups.[23] Pioglitazone plus metformin and rosiglitazone plus metformin therapy significantly (all $p < 0.01$) reduced mean levels of FPG (1.17 and 1.00 mmol/L) and PPG (1.72 and 1.28 mmol/L) by the end of the 52-week trial, from mean baseline FPG values of 8.94 and 9.10 mmol/L and PPG values of 10.71 and 10.60 mmol/L. Significant (all $p < 0.05$) reductions in both FPG and PPG levels were evident at 9 months; pioglitazone plus metformin therapy reduced mean levels of FPG and PPG from baseline by 0.89 and 1.17 mmol/L, with corresponding reductions of 0.67 and 0.89 mmol/L exhibited in recipients of rosiglitazone plus metformin.[23]

- Pioglitazone plus metformin recipients showed greater improvements in lipid control than those receiving rosiglitazone plus metformin (primary endpoint).[23] After 12 months of therapy, the mean reductions from baseline in levels of triglycerides (0.47 vs 0.03 mmol/L), LDL-C (0.21 vs 0.08 mmol/L increase) and total cholesterol (0.49 vs 0.21 mmol/L increase) were significantly (all $p < 0.05$) greater in the pioglitazone than rosiglitazone group. Respective mean baseline levels were 1.90 and 1.93 mmol/L for triglycerides, 3.00 and 2.95 mmol/L for LDL-C and 5.02 and 4.91 mmol/L for total cholesterol.[23]

• Furthermore, mean levels of HDL-C were significantly ($p < 0.05$) increased in pioglitazone plus metformin recipients but reduced in recipients of rosiglitazone plus metformin (0.10 vs −0.03 mmol/L; $p < 0.05$) from mean baseline levels of 1.14 and 1.09 mmol/L (primary endpoint).[23]

Versus a Sulphonylurea Agent plus Metformin

The efficacy of pioglitazone plus metformin has been compared with that of metformin in combination with gliclazide in a randomised, double-blind, double-dummy, 52-week trial (n = 630)[18] and its 52-week continuation,[19] with glimepiride in a randomised, open-label, parallel-group, multicentre, 28-week trial (n =203)[22] and with glibenclamide in a prospective, multicentre, 96-week trial (n = 379).[34] Data from an observational (mean observational period 3.5 years), open-label study (n = 500)[21] and a randomised, double-blind, 3-year study (n = 2120),[35] comparing pioglitazone plus metformin with glibenclamide plus metformin are also briefly discussed.

Trials were in patients with type 2 diabetes inadequately controlled with metformin monotherapy,[18,19,22] although this was not unequivocally stated in posters or oral presentations.[21,34,35] Data are fully published,[18,19,22] or have been presented in abstracts and/or posters,[21,34] or orally.[35]

Patient inclusion criteria included an HbA_{1c} of ≥7.5% to ≤11.0%,[18] 7.5–10.0%,[22] 6.5–10.0%,[34] or 9.5%,[35] fasting C-peptide levels of ≥0.5 nmol/L,[18] and/or an FPG level of 6.99–13.04 mmol/L.[22] Patients had to have stable or deteriorating glycaemic control within 3 months of screening,[18] be receiving monotherapy with metformin 1000–2500 mg/day or extended-release metformin 500–2000 mg/day for the previous 2 months[22] or already receiving metformin treatment.[21,34] At baseline, patients ranged in age from 18 to 80 years, had a mean HbA_{1c} level of ≈8.6%,[18] ≈8.35%,[22] ≈7.7%[34] or 9.5%,[35] a mean duration of diabetes of ≈5.65,[18] 6.7[34] or 4.7[21] years, and a mean FPG level of ≈11.5,[18] ≈10.10[22] or ≈9.05 mmol/L.[34] There was generally no between-group difference in baseline characteristics within each trial.

Exclusion criteria included previous treatment with insulin, sulphonylureas or thiazolidinediones within 3 months,[22] myocardial infarction or stroke within 6 months,[18] congestive heart failure[34] or were not specified.[21,35]

All agents were administered orally, with the dosage of metformin generally not reported. In addition to metformin, patients received pioglitazone 30mg[21] or titrated to 45mg once daily,[18,22,35] glimepiride 2 mg/day titrated to 8 mg/day,[22] gliclazide titrated to 240mg once daily or 160mg once or twice daily,[18] or glibenclamide 3.5mg titrated to 15 mg/day.[21] Dosages of antihyperglycaemic agents were titrated based on efficacy and/or tolerability.[18,21,22,35] Dosages were not reported in one study.[34] Where stated, the duration of the titration phase was 6[22] or 16[18] weeks. In one study,[35] insulin therapy was added if target HbA_{1c} levels were not achieved after 3 months' treatment. Where reported in one trial, there was a 2-week stabilisation phase.[22]

The primary endpoint, where stated, was the change in HbA_{1c} from baseline,[18,19,21,22,34] and was evaluated at the end of the trial;[18,22] however, the timepoint of evaluation was not specified in some studies.[19,21,34] Other efficacy variables included changes in levels of FPG[18,19,22,34] and lipids (triglycerides, HDL-C and LDL-C).[18,19,22,34] Where stated, analyses were based on the ITT population[18,19,22,34] unless otherwise specified.

Effects on Glycaemic Control

• After 52 weeks of treatment, pioglitazone (n = 317) and gliclazide (n = 313) showed similar efficacy, in combination with metformin, in terms of improving glycaemic control.[18] The changes from baseline in mean HbA_{1c} (−0.99% vs −1.01%) and FPG (−2.1 vs −1.6 mmol/L) levels were similar between pioglitazone plus metformin and gliclazide plus metformin groups after 52 weeks of therapy; respective baseline HbA_{1c} and FPG values were 8.71% and 8.53% and 11.8 and 11.3 mmol/L. The maximum changes from baseline in both HbA_{1c} and FPG levels occurred at 24 and 16 weeks with piogli-

tazone plus metformin and at 16 and 8 weeks with gliclazide plus metformin.

- Improved glycaemic control was effectively sustained with pioglitazone plus metformin during the 52-week continuation of this trial.[19] After 104 weeks of therapy, the changes from baseline in mean HbA_{1c} were not significantly different between pioglitazone and gliclazide treatment groups in the ITT population (−0.89% and −0.77%). Nonetheless, in a per-protocol analysis of patients who received ≥18 months of treatment, the mean change from baseline in HbA_{1c} was significantly greater with pioglitazone plus metformin than with gliclazide plus metformin at end of trial (−1.07% vs −0.76%; p = 0.003); changes from baseline were not significant.

- The change from baseline in mean FPG levels was significantly greater in pioglitazone plus metformin than in gliclazide plus metformin recipients in the ITT population at 104 weeks (−1.8 vs −1.1 mmol/L; p < 0.001).[19] Target HbA_{1c} levels of <7.0% were achieved by similar proportions of pioglitazone plus metformin (30.6%) and gliclazide plus metformin (25.2%) recipients.

- After 26 weeks, combination therapy with pioglitazone plus metformin (n = 107) was as effective as glimepiride plus metformin (n = 96) in terms of improvement of glycaemic control, with mean reductions in HbA_{1c} of 1.23% and 1.30% from respective baseline values of 8.31% and 8.40%.[22] Mean HbA_{1c} was significantly reduced from baseline at all timepoints in both treatment groups (all p = 0.0001). At various timepoints during the 26-week study, the reduction from baseline in HbA_{1c} levels was significantly greater in glimepiride plus metformin than pioglitazone plus metformin recipients: weeks 6 (−1.09% vs −0.51%; p = 0.0001), 12 and 20 (values not reported; both p < 0.05).[22]

- At study end, secondary endpoints also indicated that there was no difference between the two treatment groups in this trial.[22] A similar proportion of patients in both treatment groups achieved HbA_{1c} ≤7.0% at 26 weeks (55.1% vs 56.3% in the glimepiride group). There were also no differences between the two treatment groups at study end in terms of reductions in mean FPG levels (2.20 vs 1.89 mmol/L in the glimepiride plus metformin group), with both treatment groups exhibiting levels significantly reduced from baseline (10.01 vs 10.22 mg/dL) from 6 weeks onwards (all p = 0.0001).[22] There was only one timepoint during the study where the FPG level reductions were less extensive with pioglitazone plus metformin than glimepiride plus metformin treatment (with values at 6 weeks of 1.67 vs 2.30 mmol/L; p = 0.0195).[22]

- In two long-term prospective trials, pioglitazone plus metformin was at least as effective as glibenclamide plus metformin in terms of improvement in glycaemic control.[34,35] In a 3-year double-blind trial, reductions in HbA_{1c} were significantly (all p < 0.001) greater in the pioglitazone than glibenclamide group from week 72 onwards; at 156 weeks, respective changes in HbA_{1c} from baseline were −2.3% and −1.8% (values estimated from a graph; n = 323 and 333).[35] No baseline data reported in abstract presentation.[35] In the other trial,[34] there was no between-group difference in terms of improvements in HbA_{1c} levels in the ITT population at 96 weeks (−0.79% vs −0.61% in the glibenclamide group; baseline values 7.8% and 7.7%). However, in responders (i.e. patients with no switch in diabetic medication during the study), there was a greater improvement in HbA_{1c} level in the pioglitazone than in the glibenclamide group at study end (−0.85% vs −0.61%; p = 0.025).[34]

- In an observational study, pioglitazone plus metformin (n = 250) improved glycaemic control to a greater extent than glibenclamide plus metformin (n = 250) at all timepoints from 24 to 42 months (all p < 0.05).[21] At 42 months, HbA_{1c} levels had been reduced by 1% (p < 0.005) and 0.6% (p < 0.05) in the pioglitazone and glibenclamide groups, from baseline values of 8.5% and 8.6%. Moreover, fewer pioglitazone than glibenclamide recipients required additional insulin therapy (22% vs 55.2%; p < 0.001).[21]

Effects on Lipid Control

- The lipid profile of patients with type 2 diabetes poorly controlled with metformin was generally improved to a greater extent with pioglitazone than

gliclazide addition at 52[18] and 104 weeks.[19] Mean levels of triglycerides were reduced from baseline (2.90 vs 2.78 mmol/L) to a greater extent with pioglitazone plus metformin than with gliclazide plus metformin after both 52 weeks (18% vs 7%; $p < 0.001$)[18] and 104 weeks (23% vs 7%: $p < 0.001$).[19] Corresponding changes in mean LDL-C levels from baseline (3.34 vs 3.28 mmol/L) at 52 (8% vs −3%)[18] and 104 weeks (2% vs −6%)[19] were small, but favoured gliclazide plus metformin treatment ($p < 0.001$ at both timepoints). In addition, pioglitazone plus metformin recipients experienced significantly (both $p < 0.001$) greater improvements from baseline (1.10 vs 1.09 mmol/L) in mean HDL-C levels at 52 (increased by 16% vs 0%)[18] and 104 weeks (increased by 22% vs 7%)[19] than patients treated with gliclazide plus metformin.

- Pioglitazone plus metformin treatment showed similar efficacy to that of glimepiride plus metformin in terms of reducing triglyceride levels, although the efficacy of the combination therapies differed with regard to effects on HDL-C and LDL-C levels.[22] Respective triglyceride levels were reduced from baseline levels of 1.27 and 1.05 mmol/L to similar extents at 26 weeks with both therapies (0.16 vs 0.05 mmol/L). After 26 weeks of treatment, mean HDL-C levels were significantly improved from baseline (1.11 vs 1.13 mmol/L) with pioglitazone plus metformin compared with glimepiride plus metformin (0.12 vs −0.02 mmol/L; $p = 0.0001$).[22] However, mean levels of LDL-C were significantly ($p = 0.0026$) increased from baseline with pioglitazone plus metformin by end of trial but remained almost unchanged with glimepiride plus metformin (0.220 vs −0.003 mmol/L; $p = 0.0331$); respective baseline levels were 2.81 and 2.92 mmol/L.[22]

4. Tolerability

Oral pioglitazone (30 or 45mg once daily) plus metformin therapy was generally well tolerated in clinical trials of up to 3 years duration discussed in section 3,[8,18,19,22,36,37] with most treatment-emergent adverse events being of mild to moderate severity.[8,18,19] In general, only descriptive analyses were reported, with some data derived from the manufacturer's prescribing information.[9]

- Pioglitazone plus metformin exhibited a tolerability profile similar to that of placebo plus metformin, with treatment-emergent adverse events common to metformin monotherapy, including nausea, diarrhoea and epigastric discomfort, reported at a similar incidence in both pioglitazone plus metformin and placebo plus metformin groups (values not reported).[8] The most common treatment-emergent adverse events to occur in ≥5% of patients and with at least a 2% greater incidence in pioglitazone 30mg plus metformin than placebo plus metformin recipients were combined/peripheral oedema (6.0% and 2.5%) and headache (6.0% and 1.9%).[9] Few patients in either group discontinued treatment because of adverse events (3% vs 2% with placebo plus metformin).

- The tolerability profile of both dosages of pioglitazone (30 and 45mg once daily plus metformin) was generally similar, with 7.8% and 7.7% of recipients discontinuing treatment because of adverse events.[9] In a 24-week trial, the only treatment-emergent adverse events that occurred with at least a 2% higher incidence in the higher (pioglitazone 45mg plus metformin) than in the lower (pioglitazone 30mg plus metformin) dosage group were lower limb oedema (11.3% vs 2.9%) and weight gain (6.7% vs 2.9%).[9]

- The tolerability of pioglitazone plus metformin was similar to that of rosiglitazone plus metformin, with treatment-emergent adverse events reported in 8.3% and 10.4% of recipients.[23]

- Pioglitazone plus metformin was at least as well tolerated as a sulphonylurea agent plus metformin in clinical trials discussed in section 3.[18,19,22] Where reported, a similar percentage of patients in the pioglitazone plus metformin and the gliclazide plus metformin groups discontinued treatment because of adverse events (6.9% vs 6.7%).[19]

- Serious cardiac treatment-emergent adverse events were no more prevalent in patients treated with pioglitazone plus metformin than in those receiving placebo plus metformin in trials that excluded patients with a New York Heart Association

cardiac status of class III or IV.[9] Serious cardiac adverse events occurred with an incidence of 4.7% and 6.0% in pioglitazone plus metformin and glibenclamide plus metformin groups, in a 3-year safety study.[37]

- Oedema was the most common treatment-emergent adverse event to occur in patients receiving pioglitazone plus metformin in the 52-week study, occurring with an incidence of 6.3% compared with 2.2% in recipients of gliclazide plus metformin.[18] In the pioglitazone plus metformin group, one patient discontinued treatment because of oedema and in one of two patients who experienced pulmonary oedema, the adverse event was considered drug-related and severe, with myocardial infarction. An increased prevalence of heart failure was not associated with the oedema.[18] Oedema was not a reason for trial discontinuation in the placebo-controlled trial.[8]

- Hypoglycaemia occurred with a statistically[22] or numerically[18,19,38] lower incidence with pioglitazone plus metformin than with sulphonylurea plus metformin combinations. The prevalence of hypoglycaemia was significantly lower with pioglitazone plus metformin than with glimepiride plus metformin in a 28-week study (0.9% vs 33%; p = 0.0001).[22] Hypoglycaemia occurred with an incidence of 1.3% and 11.2% in the pioglitazone plus metformin and gliclazide plus metformin groups in the 52-week trial,[18] with similar results reported following a 52-week continuation of the trial.[19] Similarly, in a 3-year study, hypoglycaemia was reported by 3.8% and 11.4% of pioglitazone plus metformin and glibenclamide plus metformin recipients.[38]

- Few patients receiving pioglitazone plus metformin experienced elevated ALT levels (i.e. ≥3 times the upper limit of normal [ULN]) in clinical trials.[9] Levels returned to normal at follow-up visits, with <0.9% of patients discontinuing treatment because of abnormal liver function tests.

- The incidence of ALT levels greater than 3 × ULN was similar in pioglitazone plus metformin recipients to that in glibenclamide plus metformin recipients in a large (n > 2000), randomised, double-blind, multicentre, 3-year safety study (0.29% vs 0.86%) [primary endpoint].[36] However, fewer pioglitazone than glibenclamide recipients experienced elevations of ALT and gamma glutamyl transpeptidase >1.5 × ULN or baseline during treatment, whereas the incidence of such elevations in AST was higher in the pioglitazone group (figure 2). The mean change in ALT and AST levels from baseline also favoured the pioglitazone group (figure 2).

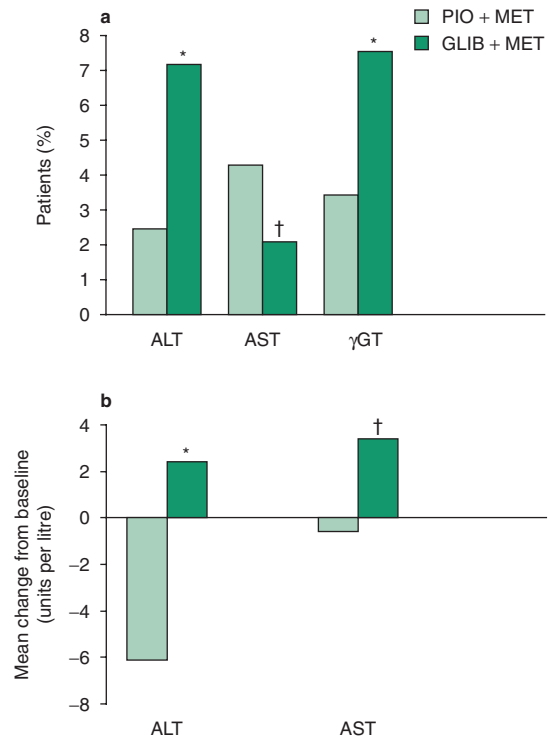

Fig. 2. Long-term effects on liver enzyme levels in recipients of oral pioglitazone (PIO) plus metformin (MET) and glibenclamide (GLIB) plus MET in patients with type 2 diabetes mellitus. (**a**) Incidence of ALT, AST and gamma glutamyl transpeptidase (γGT) levels >1.5 times the upper limit of normal or baseline and (**b**) changes from baseline in mean ALT and AST levels in PIO plus MET (n = 1051) and GLIB plus MET (n = 1046) recipients in a randomised, double-blind, multicentre, 3-year trial in patients with type 2 diabetes mellitus.[36] Dosages were titrated to PIO 45mg or GLIB 15mg; MET dosage was maximised or added to achieve glycosylated haemoglobin (HbA_{1c}) levels of <7.5% (dosage administration frequencies were not reported). If HbA_{1c} <7.5% was not achieved after 3 months, insulin therapy was initiated. * p < 0.0001; † p ≤ 0.005 vs comparator.

- Overall, there were no significant changes from baseline in levels of ALT (both +2 U/L) or AST (+3 vs 2 U/L) in recipients of pioglitazone plus metformin or rosiglitazone plus metformin after 12 months (statistical analyses were not reported); respective baseline values were 24 and 25 U/L for ALT and 22 and 23 U/L for AST.[23]
- Pioglitazone plus metformin recipients experienced small increases in bodyweight, as did patients receiving a sulphonylurea plus metformin (no statistical data reported).[8,18,19,22,38] Mean changes from baseline in bodyweight were reported with pioglitazone plus metformin and placebo plus metformin (+0.95 and −1.36kg) in a 16-week trial.[8] Such mean changes in bodyweight were also reported with pioglitazone plus metformin and gliclazide plus metformin in a 52-week trial (+1.5 and +1.4kg)[18] and its 52-week continuation (+2.5 and +1.2kg),[19] and pioglitazone plus metformin and glimepiride plus metformin in a 28-week trial (+1.74 and +1.85kg).[22]
- Pioglitazone may reduce levels of haemoglobin and haematocrit as a result of increased plasma volume; however, anaemia was documented in ≤2% of patients who received pioglitazone plus metformin in double-blind trials.[9]
- Lactic acidosis is a serious complication that may occur during treatment with metformin; however, during clinical trials there were no reported incidences of lactic acidosis in >20 000 patient-years.[9] Moreover, its reported incidence in recipients of metformin is low (≈0.03 cases per 1000 patient-years).[9]

5. Dosage and Administration

Fixed-dose pioglitazone/metformin tablets are approved in the US as an adjunct to diet and exercise in patients with type 2 diabetes already receiving combination treatment with the individual agents and in those with inadequately controlled diabetes despite treatment with either monotherapy.[9]

In the US, the initial dosage of pioglitazone/metformin should be based on the current pioglitazone and/or metformin dosage regimen of the patient, with subsequent titration according to efficacy and tolerability.[9] In patients with inadequate glycaemic control with metformin or pioglitazone monotherapy and in patients currently on combination therapy with pioglitazone plus metformin as separate agents the recommended dosage is pioglitazone/metformin 15mg/500mg or 15mg/850mg once or twice daily. The maximum recommended daily dosage is pioglitazone 45mg and metformin 2550mg.[9]

In the EU, the pioglitazone/metformin 15mg/850mg fixed-dose tablet is approved for the treatment of patients with type 2 diabetes, particularly those who are overweight, with inadequate glycaemic control with their current maximum metformin monotherapy dosage.[39] It is recommended that such patients first receive pioglitazone dosage titration in addition to their optimal metformin dosage before administration of the fixed-dose combination. The combination tablet may be taken twice daily.[40]

Local prescribing information should be consulted for further information regarding contraindications, drug interactions and other precautions.

6. Pioglitazone/Metformin: Current Status

Fixed-dose tablets of pioglitazone/metformin 15mg/500mg and 15mg/850mg are approved and have been launched in the US as adjunctive therapy in patients with type 2 diabetes already receiving combination treatment with the individual agents and in those with inadequately controlled diabetes despite treatment with either monotherapy.[9]

In the EU, the pioglitazone/metformin 15mg/850mg fixed-combination tablet has recently been approved for the treatment of type 2 diabetes in patients with inadequate glycaemic control with metformin monotherapy.[39]

In several well designed clinical trials, pioglitazone plus metformin provided effective glycaemic control and was generally well tolerated in patients with inadequately controlled type 2 diabetes despite metformin therapy. This combination was as effective as combination therapy with rosiglitazone plus metformin and was at least as effective as a sulphonylurea agent plus metformin in terms of

improvements in glycaemic control, but pioglitazone plus metformin was superior to these regimens in terms of improvements in lipid profiles.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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