ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tandemact 30 mg/2 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg of pioglitazone (as hydrochloride) and 2 mg of glimepiride.

Excipient: Each tablet contains approximately 125 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White to off-white, round, convex and embossed '4833 G' on one face and '30/2' on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tandemact is indicated as second line 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.

After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained (see section 4.4).

4.2 Posology and method of administration

If patients report hypoglycaemia, the dose of Tandemact should be reduced or free combination therapy should be considered.

If patients are receiving pioglitazone in combination with a sulphonylurea other than glimepiride, patients should be stabilised with concomitant pioglitazone and glimepiride before switching to Tandemact.

Elderly:

No dosage adjustment is necessary for elderly patients (see section 5.2). Physicians should start treatment with the lowest available dose and increase the dose gradually, particularly when pioglitazone is used in combination with insulin (see section 4.4 Fluid retention and cardiac failure).

Patients with renal impairment:

Tandemact should not be used in patients with severe renal function disorders (creatinine clearance <30 ml/min, see section 4.3).

Patients with hepatic impairment:

Tandemact should not be used in patients with hepatic impairment (see section 4.3).

Children and adolescents:

Tandemact is not recommended for use in patients below age 18 due to insufficient data on safety and efficacy.

The tablets are taken orally once daily shortly before or with the first main meal. The tablets should be swallowed whole with some liquid.

4.3 Contraindications

Tandemact is contraindicated in patients with:

- Hypersensitivity to the active substances, or to any of the excipients, or other sulphonylureas or sulphonamides
- Cardiac failure or history of cardiac failure (NYHA stages I to IV)
- Current bladder cancer or a history of bladder cancer
- Uninvestigated macroscopic haematuria
- Hepatic impairment
- Type 1 diabetes mellitus
- Diabetic coma
- Diabetic ketoacidosis
- Severe renal function disorders
- Pregnancy
- Lactation

4.4 Special warnings and precautions for use

There is no clinical trial experience of other oral anti-hyperglycaemic agents added to treatment with Tandemact or concomitantly administered glimepiride and pioglitazone.

Hypoglycaemia:

When meals are taken at irregular hours or skipped altogether, treatment with Tandemact may lead to hypoglycaemia due to the sulphonylurea component. Symptoms can almost always be promptly controlled by immediate intake of carbohydrates (sugar). Artificial sweeteners have no effect.

It is known from other sulphonylureas that, despite initially successful countermeasures, hypoglycaemia may recur. Severe hypoglycaemia or prolonged hypoglycaemia, only temporarily controlled by the usual amounts of sugar, require immediate medical treatment and occasionally hospitalisation.

Treatment with Tandemact requires regular monitoring of glycaemic control.

Fluid retention and cardiac failure:

Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction or symptomatic coronary artery disease or the elderly), physicians should start with the lowest available dose of pioglitazone and increase the dose gradually. Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with reduced cardiac reserve.

There have been cases of cardiac failure reported from the market when pioglitazone was used in combination with insulin. or in patients with a history of cardiac failure. Since insulin and pioglitazone are both associated with fluid retention, concomitant administration may increase the risk of oedema. Tandemact should be discontinued if any deterioration in cardiac state occurs.

A cardiovascular outcome study of pioglitazone has been performed in patients under 75 years with type 2 diabetes mellitus and pre-existing major macrovascular disease. Pioglitazone or placebo was added to existing antidiabetic and cardiovascular therapy for up to 3.5 years. This study showed an increase in reports of heart failure, however this did not lead to an increase in mortality in this study.

Elderly:

Combination use with insulin should be considered with caution in the elderly because of increased risk of serious heart failure.

In light of age- related risks (especially bladder cancer, fractures and heart failure), the balance of benefits and risks should be considered carefully both before and during treatment in the elderly.

Bladder Cancer:

Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12506 patients, 0.15%) than in control groups (7 cases from 10212 patients, 0.07%) HR=2.64 (95% CI 1.11-6.31, P=0.029). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Available epidemiological data also suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone in particular in patients treated for the longest durations and with the highest cumulative doses. A possible risk after short term treatment cannot be excluded.

Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic haematuria should be investigated before starting pioglitazone therapy.

Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

Liver function:

There have been rare reports of hepatocellular dysfunction during post-marketing experience with pioglitazone and glimepiride (see section 4.8). It is recommended, therefore, that patients treated with Tandemact undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with Tandemact in all patients. Therapy with Tandemact should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 X upper limit of normal) or with any other evidence of liver disease.

Following initiation of therapy with Tandemact, it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3 X upper limit of normal during Tandemact therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with Tandemact should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, therapy with Tandemact should be discontinued.

Weight gain:

In clinical trials with pioglitazone and sulphonylurea monotherapy or in combination there was evidence of dose related weight gain, which may be due to fat accumulation and in some cases associated with fluid retention. In some cases weight increase may be a symptom of cardiac failure therefore weight should be closely monitored. Part of the treatment of diabetes is dietary control. Patients should be advised to adhere strictly to a calorie-controlled diet.

Haematology:

Rare changes in haematology have been observed with glimepiride treatment (see section 4.8). Treatment with Tandemact therefore requires regular haematological monitoring (especially leucocytes and platelets).

During therapy with pioglitazone there was a small reduction in mean haemoglobin (4 % relative reduction) and haematocrit (4.1 % relative reduction), consistent with haemodilution. Similar changes were seen in metformin (haemoglobin 3 - 4 % and haematocrit 3.6 – 4.1% relative reductions) and to a lesser extent sulphonylurea and insulin (haemoglobin 1 – 2 % and haematocrit 1 – 3.2 % relative reductions) treated patients in comparative controlled trials with pioglitazone.

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since glimepiride belongs to the chemical class of sulfonylurea medicinal products, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

Eye disorders:

Post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with thiazolidinediones, including pioglitazone. Many of these patients reported concurrent peripheral oedema. It is unclear whether or not there is a direct association between pioglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity; an appropriate ophthalmological referral should be considered.

Others:

An increased incidence in bone fractures in women was seen in a pooled analysis of adverse event reports of bone fracture from randomised, controlled, double blind clinical trials in over 8100 pioglitazone and 7400 comparator treated patients, on treatment for up to 3.5 years.

Fractures were observed in 2.6% of women taking pioglitazone compared to 1.7% of women treated with a comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).

The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this dataset on pioglitazone is therefore 0.8 fractures per 100 patient years of use.

In the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%; 1.0 fractures per 100 patient years) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures per 100 patient years) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).

The risk of fractures should be considered in the long term care of women treated with pioglitazone.

As a consequence of enhancing insulin action, pioglitazone treatment in patients with polycystic ovarian syndrome may result in resumption of ovulation. These patients may be at risk of pregnancy.

Patients should be aware of the risk of pregnancy and if a patient wishes to become pregnant or if pregnancy occurs, the treatment should be discontinued (see section 4.6).

Pioglitazone should be used with caution during concomitant administration of cytochrome P450 2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin). Glycaemic control should be monitored closely. Pioglitazone dose adjustment within the recommended posology or changes in diabetic treatment should be considered (see section 4.5).

The tablets contain lactose monohydrate and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for Tandemact, however, the concomitant use of the active substances in patients in clinical use has not resulted in any unexpected interactions. The following statements reflect the information available on the individual active substances (pioglitazone and glimepiride).

Pioglitazone

Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Co-administration of pioglitazone with sulphonylureas does not appear to affect the pharmacokinetics of the sulphonylurea. Studies in man suggest no induction of the main inducible cytochrome P450, 1A, 2C8/9 and 3A4. *In vitro* studies have shown no inhibition of any subtype of cytochrome P450. Interactions with substances metabolised by these enzymes, e.g. oral contraceptives, cyclosporin, calcium channel blockers, and HMGCoA reductase inhibitors are not to be expected.

Co-administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) is reported to result in a 3-fold increase in AUC of pioglitazone. A decrease in the dose of pioglitazone may be needed when gemfibrozil is concomitantly administered. Close monitoring of glycaemic control should be considered (see section 4.4)**.** Co-administration of pioglitazone with rifampicin (an inducer of cytochrome P450 2C8) is reported to result in a 54% decrease in AUC of pioglitazone. The pioglitazone dose may need to be increased when rifampicin is concomitantly administered. Close monitoring of glycaemic control should be considered (see section 4.4).

Glimepiride

If glimepiride is taken simultaneously with certain other medicinal products, both undesired increases and decreases in the hypoglycaemic action of glimepiride can occur. For this reason, other medicinal products should only be taken with Tandemact with the knowledge (or at the prescription) of the doctor.

Based on the experience with glimepiride and with other sulphonylurea the following interactions have to be mentioned.

Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following active substances is taken, for example:
phenylbutazone, azapropazon and oxyfenbutazone
insulin and oral antidiabetic products
metformin
salicylates and p-amino-salicylic acid
anabolic steroids and male sex hormones
chloramphenicol
coumarin anticoagulants
fenfluramine

fibrates
ACE inhibitors
fluoxetine
allopurinol
sympatholytics
cyclo-, tro-and iphosphamides
sulphinpyrazone
certain long-acting sulphonamides
tetracyclines
MAO-inhibitors
quinolone antibiotics
probenecid
miconazol
pentoxyfylline (high dose parenteral)
tritoqualine
fluconazole

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following active substances is taken, for example:

oestrogens and progestagens,
saluretics, thiazide diuretics,
thyroid stimulating agents, glucocorticoids,
phenothiazine derivatives, chlorpromazine,
adrenaline and sympathicomimetics,
nicotinic acid (high dosages) and nicotinic acid derivatives,
laxatives (long-term use),
phenytoin, diazoxide,
glucagon, barbiturates and rifampicin.
acetozolamide

H_2 antagonists, betablockers, clonidine and reserpine may lead to either potentiation or weakening of the blood glucose lowering effect.

Under the influence of sympatholytic active substances such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counterregulation to hypoglycaemia may be reduced or absent.

Alcohol intake may potentiate or weaken the hypoglycaemic action of glimepiride in an unpredictable fashion.

Glimepiride may either potentiate or weaken the effects of coumarin derivatives.

4.6 Pregnancy and lactation

There are no adequate data from the use of pioglitazone and glimepiride in pregnant women. Studies of pioglitazone in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. There are no adequate data from the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which was most likely related to the pharmacological action (hypoglycaemia) of glimepiride. Tandemact must not be used during pregnancy.

Sulphonylurea-derivatives like glimepiride pass into the breast milk. Pioglitazone has been shown to be present in the milk of lactating rats. It is not known whether pioglitazone is secreted in human milk. Therefore, Tandemact must not be administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia from glimepiride or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warnings of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machines in these circumstances.

4.8 Undesirable effects

No therapeutic clinical trials have been conducted with Tandemact. However, bioequivalence of Tandemact with coadministered pioglitazone and glimepiride has been demonstrated (see section 5.2).

Adverse reactions reported in excess (> 0.5 %) of placebo and as more than an isolated case in patients receiving pioglitazone in double-blind studies in combination with a sulphonylurea, including glimepiride, are listed below as MedDRA preferred term by system organ class and absolute frequency. Frequencies are defined as: common > 1/100, < 1/10; uncommon > 1/1000, < 1/100; rare > 1/10000, < 1/1000; very rare < 1/10000; isolated reports: not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

PIOGLITAZONE IN COMBINATION THERAPY WITH SULPHONYLUREA

Ear and labyrinth disorders

Uncommon: vertigo

Eye disorders

Uncommon: visual disturbance

Gastrointestinal disorders

Common: flatulence

General disorders and administration site conditions

Uncommon: fatigue

Investigations

Common: weight increased

Uncommon: increased lactic dehydrogenase

Metabolism and nutritional disorders

Uncommon: hypoglycaemia, appetite increased

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Uncommon: bladder cancer

Nervous system disorders

Common: dizziness

Uncommon: headache

Renal and urinary disorders

Uncommon: glycosuria, proteinuria

Skin and subcutaneous tissue disorders

Uncommon: sweating

Oedema was reported in 6 – 9 % of patients treated with pioglitazone over one year in controlled clinical trials. The oedema rates for comparator groups (sulphonylurea, metformin) were 2 – 5 %. The reports of oedema were generally mild to moderate and usually did not require discontinuation of treatment.

In active comparator controlled trials mean weight increase with pioglitazone given as monotherapy was 2 – 3 kg over one year. This is similar to that seen in a sulphonylurea active comparator group. In combination trials pioglitazone added to a sulphonylurea resulted in a mean weight increase over one year of 2.8 kg.

Visual disturbance has been reported mainly early in treatment and is related to changes in blood glucose due to temporary alteration in the turgidity and refractive index of the lens as seen with other hypoglycaemic agents.

In clinical trials with pioglitazone the incidence of elevations of ALT greater than three times the upper limit of normal was equal to placebo but less than that seen in metformin or sulphonylurea comparator groups. Mean levels of liver enzymes decreased with treatment with pioglitazone. Rare cases of elevated liver enzymes and hepatocellular dysfunction have occurred in post-marketing experience. Although in very rare cases fatal outcome has been reported, causal relationship has not been established.

In controlled clinical trials the incidence of reports of heart failure with pioglitazone treatment was the same as in placebo, metformin and sulphonylurea treatment groups, but was increased when used in combination therapy with insulin. In an outcome study of patients with pre-existing major macrovascular disease, the incidence of serious heart failure was 1.6% higher with pioglitazone than with placebo, when added to therapy that included in insulin. However, this did not lead to an increase in mortality in this study. Heart failure has been reported rarely with marketing use of pioglitazone, but more frequently when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure.

Additional information on the individual active substances of the fixed dose combination

Pioglitazone

In double blind placebo controlled clinical trials with pioglitazone upper respiratory tract infection and hypoaesthesia were common; sinusitis and insomnia were uncommon.

In controlled clinical trials the incidence of reports of heart failure with pioglitazone treatment was the same as in placebo, metformin and sulphonylurea treatment groups. Heart failure has been reported rarely with marketing use of pioglitazone.

POST MARKETING DATA

Eye disorders

Macular oedema: not known

Glimepiride

Based on experience with glimepiride and with other sulphonylureas the following adverse reactions have to be mentioned.

Immune system disorders

Very rare: Allergic shock, allergic vasculitis

Blood and lymphatic system disorders

Rare: Changes in haematology

Gastro-intestinal disorders

Very rare: Vomiting, diarrhoea, nausea, abdominal pressure, feeling of fullness in the stomach, abdominal pain

Hepato-biliary disorders

Very rare: Hepatitis, impairment of liver function (with cholestasis and jaundice)

Skin and subcutaneous tissue disorders

Very rare: Hypersensitivity to light

Investigations

Very rare: Decrease in sodium serum concentrations

In very rare cases mild hypersensivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock. Hypersensitivity reactions of the skin may occur as itching, rash, and urticaria. Cross allergenicity with sulphonylureas, sulphonamides or related substances is possible.

Moderate to severe thrombocytopenia, leucopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anemia and pancyto-penia may occur. These are in general reversible upon discontinuation of medication.

Gastro-intestinal complaints are very rare and seldom lead to discontinuation of therapy.

Elevation of liver enzymes may occur. In very rare cases, impairment of liver function (e.g. with cholestasis and jaundice) may develop, as well as hepatitis which may progress to liver failure.

A pooled analysis was conducted of adverse event reports of bone fractures from randomised, comparator controlled, double blind clinical trials in over 8100 patients in the pioglitazone-treated groups and 7400 in the comparator-treated groups of up to 3.5 years duration. A higher rate of fractures was observed in women taking pioglitazone (2.6%) versus comparator (1.7%). No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).

In the 3.5 year PROactive study, 44/870 (5.1%) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).

4.9 Overdose

No case of overdose has been reported.

Patients have taken pioglitazone at higher than the recommended highest dose of 45 mg daily. The maximum reported dose of 120 mg/day for four days, then 180 mg/day for seven days was not associated with any symptoms.

After ingestion of an overdosage of glimepiride, hypoglycaemia may occur, lasting from 12 to 72 hours, and may recur after initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general observation in hospital is recommended. Nausea, vomiting and epigastric pain may occur. The hypoglycaemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, coordination problems, sleepiness, coma and convulsions.

Treatment of overdosage of Tandemact primarily consists of preventing absorption of glimepiride by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium-sulphate (laxative). If large quantities have been ingested, gastric lavage is indicated, followed by activated charcoal and sodium-sulphate. In case of (severe) overdosage hospitalization in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary by a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic.

In particular when treating hypoglycaemia due to accidental intake of Tandemact in infants and young children, the dose of glucose given must be carefully controlled to avoid the possibility of producing dangerous hyperglycaemia. Blood glucose should be closely monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of oral blood glucose lowering drugs; ATC code: A10BD06.

Tandemact combines two antihyperglycaemic agents with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: pioglitazone, a member of the thiazolidinedione class and glimepiride, a member of the sulphonylurea class. Thiazolidinediones act primarily by reducing insulin resistance and sulphonylureas primarily by inducing insulin release from pancreatic beta cells.

<u>Pioglitazone</u>

Pioglitazone effects may be mediated by a reduction of insulin resistance. Pioglitazone appears to act via activation of specific nuclear receptors (peroxisome proliferator activated receptor gamma) leading to increased insulin sensitivity of liver, fat and skeletal muscle cells in animals. Treatment with pioglitazone has been shown to reduce hepatic glucose output and to increase peripheral glucose disposal in the case of insulin resistance.

Fasting and postprandial glycaemic control is improved in patients with type 2 diabetes mellitus. The improved glycaemic control is associated with a reduction in both fasting and postprandial plasma insulin concentrations. A clinical trial of pioglitazone vs. gliclazide as monotherapy was extended to two years in order to assess time to treatment failure (defined as appearance of $HbA_{1c} \geq 8.0$ % after the first six months of therapy). Kaplan-Meier analysis showed shorter time to treatment failure in

patients treated with gliclazide, compared with pioglitazone. At two years, glycaemic control (defined as HbA_{1c} < 8.0 %) was sustained in 69 % of patients treated with pioglitazone, compared with 50 % of patients on gliclazide. In a two-year study of combination therapy comparing pioglitazone with gliclazide when added to metformin, glycaemic control measured as mean change from baseline in HbA_{1c} was similar between treatment groups after one year. The rate of deterioration of HbA_{1c} during the second year was less with pioglitazone than with gliclazide.

In a placebo controlled trial, patients with inadequate glycaemic control despite a three month insulin optimisation period were randomised to pioglitazone or placebo for 12 months. Patients receiving pioglitazone had a mean reduction in HbA_{1c} of 0.45% compared with those continuing on insulin alone, and a reduction of insulin dose in the pioglitazone treated group.

HOMA analysis shows that pioglitazone improves beta cell function as well as increasing insulin sensitivity. Two-year clinical studies have shown maintenance of this effect.

In one year clinical trials, pioglitazone consistently gave a statistically significant reduction in the albumin/creatinine ratio compared to baseline.

The effect of pioglitazone (45 mg monotherapy *vs.* placebo) was studied in a small 18-week trial in type 2 diabetics. Pioglitazone was associated with significant weight gain. Visceral fat was significantly decreased, while there was an increase in extra-abdominal fat mass. Similar changes in body fat distribution on pioglitazone have been accompanied by an improvement in insulin sensitivity. In most clinical trials, reduced total plasma triglycerides and free fatty acids, and increased HDL-cholesterol levels were observed as compared to placebo, with small, but not clinically significant increases in LDL-cholesterol levels. In clinical trials of up to two years duration, pioglitazone reduced total plasma triglycerides and free fatty acids, and increased HDL cholesterol levels, compared with placebo, metformin or gliclazide. Pioglitazone did not cause statistically significant increases in LDL cholesterol levels compared with placebo, whilst reductions were observed with metformin and gliclazide. In a 20-week study, as well as reducing fasting triglycerides, pioglitazone reduced post prandial hypertriglyceridaemia through an effect on both absorbed and hepatically synthesised triglycerides. These effects were independent of pioglitazone's effects on glycaemia and were statistically significant different to glibenclamide.

In PROactive, a cardiovascular outcome study, 5238 patients with type 2 diabetes mellitus and pre-existing major macrovascular disease were randomised to pioglitazone or placebo in addition to existing antidiabetic and cardiovascular therapy, for up to 3.5 years. The study population had an average age of 62 years; the average duration of diabetes was 9.5 years. Approximately one third of patients were receiving insulin in combination with metformin and/or a sulphonylurea. To be eligible patients had to have had one or more of the following: myocardial infarction, stroke, percutaneous cardiac intervention or coronary artery bypass graft, acute coronary syndrome, coronary artery disease, or peripheral arterial obstructive disease. Almost half of the patients had a previous myocardial infarction and approximately 20% had had a stroke. Approximately half of the study population had at least two of the cardiovascular history entry criteria. Almost all subjects (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors, angiotensin II antagonists, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates).

Although the study failed regarding its primary endpoint, which was a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, major leg amputation, coronary revascularisation and leg revascularisation, the results suggest that there are no long-term cardiovascular concerns regarding use of pioglitazone. However, the incidence of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.

Glimepiride

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells.

As with other sulphonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulphonylureas.

Insulin release:

Sulphonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarisation of the beta cell and results – by opening of calcium channels – in an increased influx of calcium into the cell. This leads to insulin release through exocytosis. Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel but which is different from the usual sulphonylurea binding site.

Extrapancreatic activity:

The extrapancreatic effects are for example an improvement of the sensitivity of the peripheral tissue for insulin and a decrease of the insulin uptake by the liver.

The uptake of glucose from blood into peripheral muscle and fat tissues occurs via a special transport proteins, located in the cells membrane. The transport of glucose in these tissues is the rate limiting step in the use of glucose. Glimepiride increases very rapidly the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulated glucose uptake. Glimepiride increases the activity of the glycosyl-phosphatidylinositol-specific phospholipase C which may be correlated with the induced lipogenesis and glycogenesis in isolated fat and muscle cells. Glimepiride inhibits the glucose production in the liver by increasing the intracellular concentration of fructose-2,6-bisphosphate, which in turn inhibits the gluconeogenesis.

General:

In healthy persons, the minimum effective oral dose is approximately 0.6 mg. The effect of glimepiride is dose-dependent and reproducible. The physiological response to acute physical exercise, reduction of insulin secretion, is still present under glimepiride.

There was no significant difference in effect regardless of whether glimepiride was given 30 minutes or immediately before a meal. In diabetic patients, good metabolic control over 24 hours can be achieved with a single daily dose.

Although the hydroxy metabolite of glimepiride caused a small but significant decrease in serum glucose in healthy persons, it accounts for only a minor part of the total effect.

5.2 Pharmacokinetic properties

Tandemact

Studies in human volunteers have shown Tandemact to be bioequivalent to the administration of pioglitazone and glimepiride given as separate tablets.

The following statements reflect the pharmacokinetic properties of the individual active substances of Tandemact

Pioglitazone

Absorption:

Following oral administration, pioglitazone is rapidly absorbed, and peak plasma concentrations of unchanged pioglitazone are usually achieved 2 hours after administration. Proportional increases of the plasma concentration were observed for doses from 2 - 60 mg. Steady state is achieved after

4-7 days of dosing. Repeated dosing does not result in accumulation of the compound or metabolites. Absorption is not influenced by food intake. Absolute bioavailability is greater than 80 %.

Distribution:

The estimated volume of distribution in humans is 0.25 l/kg.

Pioglitazone and all active metabolites are extensively bound to plasma protein (> 99 %).

Metabolism:

Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 although other isoforms may be involved to a lesser degree. Three of the six identified metabolites are active (M-II, M-III, and M-IV). When activity, concentrations and protein binding are taken into account, pioglitazone and metabolite M-III contribute equally to efficacy. On this basis M-IV contribution to efficacy is approximately three-fold that of pioglitazone, whilst the relative efficacy of M-II is minimal.

In vitro studies have shown no evidence that pioglitazone inhibits any subtype of cytochrome P450. There is no induction of the main inducible P450 isoenzymes 1A, 2C8/9, and 3A4 in man.

Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Concomitant administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) or with rifampicin (an inducer of cytochrome P450 2C8) is reported to increase or decrease, respectively, the plasma concentration of pioglitazone (see section 4.5).

Elimination:

Following oral administration of radiolabelled pioglitazone to man, recovered label was mainly in faeces (55%) and a lesser amount in urine (45 %). In animals, only a small amount of unchanged pioglitazone can be detected in either urine or faeces. The mean plasma elimination half-life of unchanged pioglitazone in man is 5 to 6 hours and for its total active metabolites 16 to 23 hours.

Elderly:

Steady state pharmacokinetics are similar in patients age 65 and over and young subjects.

Patients with renal impairment:

In patients with renal impairment, plasma concentrations of pioglitazone and its metabolites are lower than those seen in subjects with normal renal function, but oral clearance of parent substance is similar. Thus free (unbound) pioglitazone concentration is unchanged.

Patients with hepatic impairment:

Total plasma concentration of pioglitazone is unchanged, but with an increased volume of distribution. Intrinsic clearance is therefore reduced, coupled with a higher unbound fraction of pioglitazone.

Glimepiride

Absorption:

The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations (C_{max}) are reached approximately 2.5 hours after oral intake (mean 0.3 µg/ml during multiple dosing

of 4 mg daily) and there is a linear relationship between dose and both C_{max} and AUC (area under the time/concentration curve).

Distribution:

Glimepiride has a very low distribution volume (approximately 8.8 litres) which is roughly equal to the albumin distribution space, high protein binding (> 99%), and a low clearance (approximately 48 ml/min).

In animals, glimepiride is excreted in milk. Glimepiride is transferred to the placenta. Passage of the blood brain barrier is low.

Biotransformation and elimination:

Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted.

After a single dose of radiolabelled glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites – most probably resulting from hepatic metabolism (major enzyme is CYP2C9) – were identified both in urine and faeces: the hydroxy derivative and the carboxy derivative. After oral administration of glimepiride, the terminal half-lives of those metabolites were 3 to 6 and 5 to 6 hours respectively.

Comparison of single and multiple once-daily dosing revealed no significant differences in pharmacokinetics, and the intra-individual variability was very low. There was no relevant accumulation.

Pharmacokinetics were similar in males and females, as well as in young and elderly (above 65 years) patients. In patients with low creatinine clearance, there was a tendency for glimepiride clearance to increase and for average serum concentrations to decrease, most probably resulting from a more rapid elimination because of lower protein binding. Renal elimination of the two metabolites was impaired. Overall no additional risk of accumulation is to be assumed in such patients.

Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

5.3 Preclinical safety data

No animal studies have been conducted with the combined products of Tandemact. The following data are findings in studies performed with pioglitazone or glimepiride individually.

Pioglitazone

In toxicology studies, plasma volume expansion with haemodilution, anaemia, and reversible eccentric cardiac hypertrophy was consistently apparent after repeated dosing of mice, rats, dogs, and monkeys. In addition, increased fatty deposition and infiltration were observed. These findings were observed across species at plasma concentrations ≤ 4 times the clinical exposure. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth.

Pioglitazone was devoid of genotoxic potential in a comprehensive battery of *in vivo* and *in vitro* genotoxicity assays. An increased incidence of hyperplasia (males and females) and tumours (males) of the urinary bladder epithelium was apparent in rats treated with pioglitazone for up to 2 years.

The formation and presence of urinary calculi with subsequent irritation and hyperplasia was postulated as the mechanistic basis for the observed tumourigenic response in the male rat. A

24-month mechanistic study in male rats demonstrated that administration of pioglitazone resulted in an increased incidence of hyperplastic changes in the bladder. Dietary acidification significantly decreased but did not abolish the incidence of tumours. The presence of microcrystals exacerbated the hyperplastic response but was not considered to be the primary cause of hyperplastic changes. The relevance to humans of the tumourigenic findings in the male rat cannot be excluded.

There was no tumorigenic response in mice of either sex. Hyperplasia of the urinary bladder was not seen in dogs or monkeys treated with pioglitazone for up to 12 months.

In an animal model of familial adenomatous polyposis (FAP), treatment with two other thiazolidinediones increased tumour multiplicity in the colon. The relevance of this finding is unknown.

Glimepiride

Preclinical effects observed occurred at exposures sufficiently in excess of the maximum human exposure as to indicate little relevance to clinical use, or were due to the pharmacodynamic action (hypoglycaemia) of the compound. This finding is based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproduction toxicity studies. In the latter (covering embryotoxicity, teratogenicity and developmental toxicity), undesirable effects observed were considered to be secondary to the hypoglycaemic effects induced by the compound in dams and in offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline
Croscarmellose sodium
Hydroxypropylcellulose
Lactose monohydrate
Magnesium stearate
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blisters; packs of 14, 28, 30, 50, 90 or 98 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Takeda Global Research and Development Centre (Europe) Ltd
61 Aldwych
London
WC2B 4AE
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/06/366/017-22

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th January 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Tandemact 30 mg/4 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg of pioglitazone (as hydrochloride) and 4 mg of glimepiride.

Excipient: Each tablet contains approximately 177 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White to off-white, round, convex and embossed '4833 G' on one face and '30/4' on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tandemact is indicated as second line 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.

After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained (see section 4.4).

4.2 Posology and method of administration

If patients report hypoglycaemia, the dose of Tandemact should be reduced or free combination therapy should be considered.

If patients are receiving pioglitazone in combination with a sulphonylurea other than glimepiride, patients should be stabilised with concomitant pioglitazone and glimepiride before switching to Tandemact.

Elderly:

No dosage adjustment is necessary for elderly patients (see section 5.2). Physicians should start treatment with the lowest available dose and increase the dose gradually, particularly when pioglitazone is used in combination with insulin (see section 4.4 Fluid retention and cardiac failure).

Patients with renal impairment:

Tandemact should not be used in patients with severe renal function disorders (creatinine clearance <30 ml/min, see section 4.3).

Patients with hepatic impairment:

Tandemact should not be used in patients with hepatic impairment (see section 4.3).

Children and adolescents:

Tandemact is not recommended for use in patients below age 18 due to insufficient data on safety and efficacy.

The tablets are taken orally once daily shortly before or with the first main meal. The tablets should be swallowed whole with some liquid.

4.3 Contraindications

Tandemact is contraindicated in patients with:

- Hypersensitivity to the active substances, or to any of the excipients, or other sulphonylureas or sulphonamides
- Cardiac failure or history of cardiac failure (NYHA stages I to IV)
- Current bladder cancer or a history of bladder cancer
- Uninvestigated macroscopic haematuria
- Hepatic impairment
- Type 1 diabetes mellitus
- Diabetic coma
- Diabetic ketoacidosis
- Severe renal function disorders
- Pregnancy
- Lactation

4.4 Special warnings and precautions for use

There is no clinical trial experience of other oral anti-hyperglycaemic agents added to treatment with Tandemact or concomitantly administered glimepiride and pioglitazone.

Hypoglycaemia:

When meals are taken at irregular hours or skipped altogether, treatment with Tandemact may lead to hypoglycaemia due to the sulphonylurea component. Symptoms can almost always be promptly controlled by immediate intake of carbohydrates (sugar). Artificial sweeteners have no effect.

It is known from other sulphonylureas that, despite initially successful countermeasures, hypoglycaemia may recur. Severe hypoglycaemia or prolonged hypoglycaemia, only temporarily controlled by the usual amounts of sugar, require immediate medical treatment and occasionally hospitalisation.

Treatment with Tandemact requires regular monitoring of glycaemic control.

Fluid retention and cardiac failure:

Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction or symptomatic coronary artery disease or the elderly), physicians should start with the lowest available dose of pioglitazone and increase the dose gradually. Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with reduced cardiac reserve.

There have been cases of cardiac failure reported from the market when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure. Since insulin and pioglitazone are both associated with fluid retention, concomitant administration may increase the risk of oedema. Tandemact should be discontinued if any deterioration in cardiac state occurs.

A cardiovascular outcome study of pioglitazone has been performed in patients under 75 years with type 2 diabetes mellitus and pre-existing major macrovascular disease. Pioglitazone or placebo was added to existing antidiabetic and cardiovascular therapy for up to 3.5 years. This study showed an increase in reports of heart failure, however this did not lead to an increase in mortality in this study.

Elderly:

Combination use with insulin should be considered with caution in the elderly because of increased risk of serious heart failure.

In light of age- related risks (especially bladder cancer, fractures and heart failure), the balance of benefits and risks should be considered carefully both before and during treatment in the elderly.

Bladder cancer:

Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12506 patients, 0.15%) than in control groups (7 cases from 10212 patients, 0.07%) HR=2.64 (95% CI 1.11-6.31, P=0.029). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Available epidemiological data also suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone in particular in patients treated for the longest durations and with the highest cumulative doses. A possible risk after short term treatment cannot be excluded.

Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic haematuria should be investigated before starting pioglitazone therapy.

Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

Liver function:

There have been rare reports of hepatocellular dysfunction during post-marketing experience with pioglitazone and glimepiride (see section 4.8). It is recommended, therefore, that patients treated with Tandemact undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with Tandemact in all patients. Therapy with Tandemact should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 X upper limit of normal) or with any other evidence of liver disease.

Following initiation of therapy with Tandemact, it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3 X upper limit of normal during Tandemact therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with Tandemact should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, therapy with Tandemact should be discontinued.

Weight gain:

In clinical trials with pioglitazone and sulphonylurea monotherapy or in combination there was evidence of dose related weight gain, which may be due to fat accumulation and in some cases associated with fluid retention. In some cases weight increase may be a symptom of cardiac failure therefore weight should be closely monitored. Part of the treatment of diabetes is dietary control. Patients should be advised to adhere strictly to a calorie-controlled diet.

Haematology:

Rare changes in haematology have been observed with glimepiride treatment (see section 4.8). Treatment with Tandemact therefore requires regular haematological monitoring (especially leucocytes and platelets).

During therapy with pioglitazone there was a small reduction in mean haemoglobin (4 % relative reduction) and haematocrit (4.1 % relative reduction), consistent with haemodilution. Similar changes were seen in metformin (haemoglobin 3 - 4 % and haematocrit 3.6 – 4.1 % relative reductions) and to a lesser extent sulphonylurea and insulin (haemoglobin 1 - 2 % and haematocrit 1 - 3.2 % relative reductions) treated patients in comparative controlled trials with pioglitazone.

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since glimepiride belongs to the chemical class of sulfonylurea medicinal products, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

Eye disorders:

Post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with thiazolidinediones, including pioglitazone. Many of these patients reported concurrent peripheral oedema. It is unclear whether or not there is a direct association between pioglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity; an appropriate ophthalmological referral should be considered.

Others:

An increased incidence in bone fractures in women was seen in a pooled analysis of adverse event reports of bone fracture from randomised, controlled, double blind clinical trials in over 8100 pioglitazone and 7400 comparator treated patients, on treatment for up to 3.5 years.

Fractures were observed in 2.6% of women taking pioglitazone compared to 1.7% of women treated with a comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).

The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this dataset on pioglitazone is therefore 0.8 fractures per 100 patient years of use.

In the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%; 1.0 fractures per 100 patient years) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures per 100 patient years) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).

The risk of fractures should be considered in the long term care of women treated with pioglitazone.

As a consequence of enhancing insulin action, pioglitazone treatment in patients with polycystic ovarian syndrome may result in resumption of ovulation. These patients may be at risk of pregnancy.

Patients should be aware of the risk of pregnancy and if a patient wishes to become pregnant or if pregnancy occurs, the treatment should be discontinued (see section 4.6).

Pioglitazone should be used with caution during concomitant administration of cytochrome P450 2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin). Glycaemic control should be monitored closely. Pioglitazone dose adjustment within the recommended posology or changes in diabetic treatment should be considered (see section 4.5).

The tablets contain lactose monohydrate and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for Tandemact, however, the concomitant use of the active substances in patients in clinical use has not resulted in any unexpected interactions. The following statements reflect the information available on the individual active substances (pioglitazone and glimepiride).

Pioglitazone

Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Co-administration of pioglitazone with sulphonylureas does not appear to affect the pharmacokinetics of the sulphonylurea. Studies in man suggest no induction of the main inducible cytochrome P450, 1A, 2C8/9 and 3A4. *In vitro* studies have shown no inhibition of any subtype of cytochrome P450. Interactions with substances metabolised by these enzymes, e.g. oral contraceptives, cyclosporin, calcium channel blockers, and HMGCoA reductase inhibitors are not to be expected.

Co-administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) is reported to result in a 3-fold increase in AUC of pioglitazone. A decrease in the dose of pioglitazone may be needed when gemfibrozil is concomitantly administered. Close monitoring of glycaemic control should be considered (see section 4.4)**.** Co-administration of pioglitazone with rifampicin (an inducer of cytochrome P450 2C8) is reported to result in a 54% decrease in AUC of pioglitazone. The pioglitazone dose may need to be increased when rifampicin is concomitantly administered. Close monitoring of glycaemic control should be considered (see section 4.4).

Glimepiride

If glimepiride is taken simultaneously with certain other medicinal products, both undesired increases and decreases in the hypoglycaemic action of glimepiride can occur. For this reason, other medicinal products should only be taken with Tandemact with the knowledge (or at the prescription) of the doctor.

Based on the experience with glimepiride and with other sulphonylurea the following interactions have to be mentioned.

Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following active substances is taken, for example:
phenylbutazone, azapropazon and oxyfenbutazone
insulin and oral antidiabetic products
metformin
salicylates and p-amino-salicylic acid
anabolic steroids and male sex hormones
chloramphenicol
coumarin anticoagulants
fenfluramine

fibrates
ACE inhibitors
fluoxetine
allopurinol
sympatholytics
cyclo-, tro-and iphosphamides
sulphinpyrazone
certain long-acting sulphonamides
tetracyclines
MAO-inhibitors
quinolone antibiotics
probenecid
miconazol
pentoxyfylline (high dose parenteral)
tritoqualine
fluconazole

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following active substances is taken, for example:

oestrogens and progestagens,
saluretics, thiazide diuretics,
thyroid stimulating agents, glucocorticoids,
phenothiazine derivatives, chlorpromazine,
adrenaline and sympathicomimetics,
nicotinic acid (high dosages) and nicotinic acid derivatives,
laxatives (long-term use),
phenytoin, diazoxide,
glucagon, barbiturates and rifampicin.
acetozolamide

H_2 antagonists, betablockers, clonidine and reserpine may lead to either potentiation or weakening of the blood glucose lowering effect.

Under the influence of sympatholytic active substances such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counterregulation to hypoglycaemia may be reduced or absent.

Alcohol intake may potentiate or weaken the hypoglycaemic action of glimepiride in an unpredictable fashion.

Glimepiride may either potentiate or weaken the effects of coumarin derivatives.

4.6 Pregnancy and lactation

There are no adequate data from the use of pioglitazone and glimepiride in pregnant women. Studies of pioglitazone in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. There are no adequate data from the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which was most likely related to the pharmacological action (hypoglycaemia) of glimepiride. Tandemact must not be used during pregnancy.

Sulphonylurea-derivatives like glimepiride pass into the breast milk. Pioglitazone has been shown to be present in the milk of lactating rats. It is not known whether pioglitazone is secreted in human milk. Therefore, Tandemact must not be administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia from glimepiride or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warnings of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machines in these circumstances.

4.8 Undesirable effects

No therapeutic clinical trials have been conducted with Tandemact. However, bioequivalence of Tandemact with coadministered pioglitazone and glimepiride has been demonstrated (see section 5.2).

Adverse reactions reported in excess (> 0.5 %) of placebo and as more than an isolated case in patients receiving pioglitazone in double-blind studies in combination with a sulphonylurea, including glimepiride, are listed below as MedDRA preferred term by system organ class and absolute frequency. Frequencies are defined as: common > 1/100, < 1/10; uncommon > 1/1000, < 1/100; rare > 1/10000, < 1/1000; very rare < 1/10000; isolated reports: not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

PIOGLITAZONE IN COMBINATION THERAPY WITH SULPHONYLUREA

Ear and labyrinth disorders

Uncommon: vertigo

Eye disorders

Uncommon: visual disturbance

Gastrointestinal disorders

Common: flatulence

General disorders and administration site conditions

Uncommon: fatigue

Investigations

Common: weight increased

Uncommon: increased lactic dehydrogenase

Metabolism and nutritional disorders

Uncommon: hypoglycaemia, appetite increased

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Uncommon: bladder cancer

Nervous system disorders

Common: dizziness

Uncommon: headache

Renal and urinary disorders

Uncommon: glycosuria, proteinuria

Skin and subcutaneous tissue disorders

Uncommon: sweating

Oedema was reported in 6 - 9 % of patients treated with pioglitazone over one year in controlled clinical trials. The oedema rates for comparator groups (sulphonylurea, metformin) were 2 - 5 %. The reports of oedema were generally mild to moderate and usually did not require discontinuation of treatment.

In active comparator controlled trials mean weight increase with pioglitazone given as monotherapy was 2 - 3 kg over one year. This is similar to that seen in a sulphonylurea active comparator group. In combination trials pioglitazone added to a sulphonylurea resulted in a mean weight increase over one year of 2.8 kg.

Visual disturbance has been reported mainly early in treatment and is related to changes in blood glucose due to temporary alteration in the turgidity and refractive index of the lens as seen with other hypoglycaemic agents.

In clinical trials with pioglitazone the incidence of elevations of ALT greater than three times the upper limit of normal was equal to placebo but less than that seen in metformin or sulphonylurea comparator groups. Mean levels of liver enzymes decreased with treatment with pioglitazone. Rare cases of elevated liver enzymes and hepatocellular dysfunction have occurred in post-marketing experience. Although in very rare cases fatal outcome has been reported, causal relationship has not been established.

In controlled clinical trials the incidence of reports of heart failure with pioglitazone treatment was the same as in placebo, metformin and sulphonylurea treatment groups, but was increased when used in combination therapy with insulin. In an outcome study of patients with pre-existing major macrovascular disease, the incidence of serious heart failure was 1.6% higher with pioglitazone than with placebo, when added to therapy that included in insulin. However, this did not lead to an increase in mortality in this study. Heart failure has been reported rarely with marketing use of pioglitazone, but more frequently when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure.

Additional information on the individual active substances of the fixed dose combination

Pioglitazone

In double blind placebo controlled clinical trials with pioglitazone upper respiratory tract infection and hypoaesthesia were common; sinusitis and insomnia were uncommon.

In controlled clinical trials the incidence of reports of heart failure with pioglitazone treatment was the same as in placebo, metformin and sulphonylurea treatment groups. Heart failure has been reported rarely with marketing use of pioglitazone.

POST MARKETING DATA

Eye disorders

Macular oedema: not known

Glimepiride

Based on experience with glimepiride and with other sulphonylureas the following adverse reactions have to be mentioned.

Immune system disorders

Very rare: Allergic shock, allergic vasculitis

Blood and lymphatic system disorders

Rare: Changes in haematology

Gastro-intestinal disorders

Very rare: Vomiting, diarrhoea, nausea, abdominal pressure, feeling of fullness in the stomach, abdominal pain

Hepato-biliary disorders

Very rare: Hepatitis, impairment of liver function (with cholestasis and jaundice)

Skin and subcutaneous tissue disorders

Very rare: Hypersensitivity to light

Investigations

Very rare: Decrease in sodium serum concentrations

In very rare cases mild hypersensivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock. Hypersensitivity reactions of the skin may occur as itching, rash, and urticaria. Cross allergenicity with sulphonylureas, sulphonamides or related substances is possible.

Moderate to severe thrombocytopenia, leucopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anemia and pancyto-penia may occur. These are in general reversible upon discontinuation of medication.

Gastro-intestinal complaints are very rare and seldom lead to discontinuation of therapy.

Elevation of liver enzymes may occur. In very rare cases, impairment of liver function (e.g. with cholestasis and jaundice) may develop, as well as hepatitis which may progress to liver failure.

A pooled analysis was conducted of adverse event reports of bone fractures from randomised, comparator controlled, double blind clinical trials in over 8100 patients in the pioglitazone-treated groups and 7400 in the comparator-treated groups of up to 3.5 years duration. A higher rate of fractures was observed in women taking pioglitazone (2.6%) versus comparator (1.7%). No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).

In the 3.5 year PROactive study, 44/870 (5.1%) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).

4.9 Overdose

No case of overdose has been reported.

Patients have taken pioglitazone at higher than the recommended highest dose of 45 mg daily. The maximum reported dose of 120 mg/day for four days, then 180 mg/day for seven days was not associated with any symptoms.

After ingestion of an overdosage of glimepiride, hypoglycaemia may occur, lasting from 12 to 72 hours, and may recur after initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general observation in hospital is recommended. Nausea, vomiting and epigastric pain may occur. The hypoglycaemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, coordination problems, sleepiness, coma and convulsions.

Treatment of overdosage of Tandemact primarily consists of preventing absorption of glimepiride by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium-sulphate (laxative). If large quantities have been ingested, gastric lavage is indicated, followed by activated charcoal and sodium-sulphate. In case of (severe) overdosage hospitalization in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary by a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic.

In particular when treating hypoglycaemia due to accidental intake of Tandemact in infants and young children, the dose of glucose given must be carefully controlled to avoid the possibility of producing dangerous hyperglycaemia. Blood glucose should be closely monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of oral blood glucose lowering drugs; ATC code: A10BD06.

Tandemact combines two antihyperglycaemic agents with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: pioglitazone, a member of the thiazolidinedione class and glimepiride, a member of the sulphonylurea class. Thiazolidinediones act primarily by reducing insulin resistance and sulphonylureas primarily by inducing insulin release from pancreatic beta cells.

<u>Pioglitazone</u>

Pioglitazone effects may be mediated by a reduction of insulin resistance. Pioglitazone appears to act via activation of specific nuclear receptors (peroxisome proliferator activated receptor gamma) leading to increased insulin sensitivity of liver, fat and skeletal muscle cells in animals. Treatment with pioglitazone has been shown to reduce hepatic glucose output and to increase peripheral glucose disposal in the case of insulin resistance.

Fasting and postprandial glycaemic control is improved in patients with type 2 diabetes mellitus. The improved glycaemic control is associated with a reduction in both fasting and postprandial plasma insulin concentrations. A clinical trial of pioglitazone vs. gliclazide as monotherapy was extended to two years in order to assess time to treatment failure (defined as appearance of $HbA_{1c} \geq 8.0$ % after the first six months of therapy). Kaplan-Meier analysis showed shorter time to treatment failure in

patients treated with gliclazide, compared with pioglitazone. At two years, glycaemic control (defined as HbA_{1c} < 8.0 %) was sustained in 69 % of patients treated with pioglitazone, compared with 50 % of patients on gliclazide. In a two-year study of combination therapy comparing pioglitazone with gliclazide when added to metformin, glycaemic control measured as mean change from baseline in HbA_{1c} was similar between treatment groups after one year. The rate of deterioration of HbA_{1c} during the second year was less with pioglitazone than with gliclazide.

In a placebo controlled trial, patients with inadequate glycaemic control despite a three month insulin optimisation period were randomised to pioglitazone or placebo for 12 months. Patients receiving pioglitazone had a mean reduction in HbA_{1c} of 0.45% compared with those continuing on insulin alone, and a reduction of insulin dose in the pioglitazone treated group.

HOMA analysis shows that pioglitazone improves beta cell function as well as increasing insulin sensitivity. Two-year clinical studies have shown maintenance of this effect.

In one year clinical trials, pioglitazone consistently gave a statistically significant reduction in the albumin/creatinine ratio compared to baseline.

The effect of pioglitazone (45 mg monotherapy *vs.* placebo) was studied in a small 18-week trial in type 2 diabetics. Pioglitazone was associated with significant weight gain. Visceral fat was significantly decreased, while there was an increase in extra-abdominal fat mass. Similar changes in body fat distribution on pioglitazone have been accompanied by an improvement in insulin sensitivity. In most clinical trials, reduced total plasma triglycerides and free fatty acids, and increased HDL-cholesterol levels were observed as compared to placebo, with small, but not clinically significant increases in LDL-cholesterol levels. In clinical trials of up to two years duration, pioglitazone reduced total plasma triglycerides and free fatty acids, and increased HDL cholesterol levels, compared with placebo, metformin or gliclazide. Pioglitazone did not cause statistically significant increases in LDL cholesterol levels compared with placebo, whilst reductions were observed with metformin and gliclazide. In a 20-week study, as well as reducing fasting triglycerides, pioglitazone reduced post prandial hypertriglyceridaemia through an effect on both absorbed and hepatically synthesised triglycerides. These effects were independent of pioglitazone's effects on glycaemia and were statistically significant different to glibenclamide.

In PROactive, a cardiovascular outcome study, 5238 patients with type 2 diabetes mellitus and pre-existing major macrovascular disease were randomised to pioglitazone or placebo in addition to existing antidiabetic and cardiovascular therapy, for up to 3.5 years. The study population had an average age of 62 years; the average duration of diabetes was 9.5 years. Approximately one third of patients were receiving insulin in combination with metformin and/or a sulphonylurea. To be eligible patients had to have had one or more of the following: myocardial infarction, stroke, percutaneous cardiac intervention or coronary artery bypass graft, acute coronary syndrome, coronary artery disease, or peripheral arterial obstructive disease. Almost half of the patients had a previous myocardial infarction and approximately 20% had had a stroke. Approximately half of the study population had at least two of the cardiovascular history entry criteria. Almost all subjects (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors, angiotensin II antagonists, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates).

Although the study failed regarding its primary endpoint, which was a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, major leg amputation, coronary revascularisation and leg revascularisation, the results suggest that there are no long-term cardiovascular concerns regarding use of pioglitazone. However, the incidence of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.

Glimepiride

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells.

As with other sulphonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulphonylureas.

Insulin release:

Sulphonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarisation of the beta cell and results – by opening of calcium channels – in an increased influx of calcium into the cell. This leads to insulin release through exocytosis. Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel but which is different from the usual sulphonylurea binding site.

Extrapancreatic activity:

The extrapancreatic effects are for example an improvement of the sensitivity of the peripheral tissue for insulin and a decrease of the insulin uptake by the liver.

The uptake of glucose from blood into peripheral muscle and fat tissues occurs via a special transport proteins, located in the cells membrane. The transport of glucose in these tissues is the rate limiting step in the use of glucose. Glimepiride increases very rapidly the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulated glucose uptake. Glimepiride increases the activity of the glycosyl-phosphatidylinositol-specific phospholipase C which may be correlated with the induced lipogenesis and glycogenesis in isolated fat and muscle cells. Glimepiride inhibits the glucose production in the liver by increasing the intracellular concentration of fructose-2,6-bisphosphate, which in turn inhibits the gluconeogenesis.

General:

In healthy persons, the minimum effective oral dose is approximately 0.6 mg. The effect of glimepiride is dose-dependent and reproducible. The physiological response to acute physical exercise, reduction of insulin secretion, is still present under glimepiride.

There was no significant difference in effect regardless of whether glimepiride was given 30 minutes or immediately before a meal. In diabetic patients, good metabolic control over 24 hours can be achieved with a single daily dose.

Although the hydroxy metabolite of glimepiride caused a small but significant decrease in serum glucose in healthy persons, it accounts for only a minor part of the total effect.

5.2 Pharmacokinetic properties

Tandemact

Studies in human volunteers have shown Tandemact to be bioequivalent to the administration of pioglitazone and glimepiride given as separate tablets.

The following statements reflect the pharmacokinetic properties of the individual active substances of Tandemact

Pioglitazone

Absorption:

Following oral administration, pioglitazone is rapidly absorbed, and peak plasma concentrations of unchanged pioglitazone are usually achieved 2 hours after administration. Proportional increases of the plasma concentration were observed for doses from 2 - 60 mg. Steady state is achieved after 4–

7 days of dosing. Repeated dosing does not result in accumulation of the compound or metabolites. Absorption is not influenced by food intake. Absolute bioavailability is greater than 80 %.

Distribution:

The estimated volume of distribution in humans is 0.25 l/kg.

Pioglitazone and all active metabolites are extensively bound to plasma protein (> 99 %).

Metabolism:

Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 although other isoforms may be involved to a lesser degree. Three of the six identified metabolites are active (M-II, M-III, and M-IV). When activity, concentrations and protein binding are taken into account, pioglitazone and metabolite M-III contribute equally to efficacy. On this basis M-IV contribution to efficacy is approximately three-fold that of pioglitazone, whilst the relative efficacy of M-II is minimal.

In vitro studies have shown no evidence that pioglitazone inhibits any subtype of cytochrome P450. There is no induction of the main inducible P450 isoenzymes 1A, 2C8/9, and 3A4 in man.

Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Concomitant administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) or with rifampicin (an inducer of cytochrome P450 2C8) is reported to increase or decrease, respectively, the plasma concentration of pioglitazone (see section 4.5).

Elimination:

Following oral administration of radiolabelled pioglitazone to man, recovered label was mainly in faeces (55%) and a lesser amount in urine (45%). In animals, only a small amount of unchanged pioglitazone can be detected in either urine or faeces. The mean plasma elimination half-life of unchanged pioglitazone in man is 5 to 6 hours and for its total active metabolites 16 to 23 hours.

Elderly:

Steady state pharmacokinetics are similar in patients age 65 and over and young subjects.

Patients with renal impairment:

In patients with renal impairment, plasma concentrations of pioglitazone and its metabolites are lower than those seen in subjects with normal renal function, but oral clearance of parent substance is similar. Thus free (unbound) pioglitazone concentration is unchanged.

Patients with hepatic impairment:

Total plasma concentration of pioglitazone is unchanged, but with an increased volume of distribution. Intrinsic clearance is therefore reduced, coupled with a higher unbound fraction of pioglitazone.

Glimepiride

Absorption:

The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations (C_{max}) are reached approximately 2.5 hours after oral intake (mean 0.3 µg/ml during multiple dosing

of 4 mg daily) and there is a linear relationship between dose and both C_{max} and AUC (area under the time/concentration curve).

Distribution:

Glimepiride has a very low distribution volume (approximately 8.8 litres) which is roughly equal to the albumin distribution space, high protein binding (> 99%), and a low clearance (approximately 48 ml/min).

In animals, glimepiride is excreted in milk. Glimepiride is transferred to the placenta. Passage of the blood brain barrier is low.

Biotransformation and elimination:

Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted.

After a single dose of radiolabelled glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites – most probably resulting from hepatic metabolism (major enzyme is CYP2C9) – were identified both in urine and faeces: the hydroxy derivative and the carboxy derivative. After oral administration of glimepiride, the terminal half-lives of those metabolites were 3 to 6 and 5 to 6 hours respectively.

Comparison of single and multiple once-daily dosing revealed no significant differences in pharmacokinetics, and the intra-individual variability was very low. There was no relevant accumulation.

Pharmacokinetics were similar in males and females, as well as in young and elderly (above 65 years) patients. In patients with low creatinine clearance, there was a tendency for glimepiride clearance to increase and for average serum concentrations to decrease, most probably resulting from a more rapid elimination because of lower protein binding. Renal elimination of the two metabolites was impaired. Overall no additional risk of accumulation is to be assumed in such patients.

Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

5.3 Preclinical safety data

No animal studies have been conducted with the combined products of Tandemact. The following data are findings in studies performed with pioglitazone or glimepiride individually.

Pioglitazone

In toxicology studies, plasma volume expansion with haemodilution, anaemia, and reversible eccentric cardiac hypertrophy was consistently apparent after repeated dosing of mice, rats, dogs, and monkeys. In addition, increased fatty deposition and infiltration were observed. These findings were observed across species at plasma concentrations ≤ 4 times the clinical exposure. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth.

Pioglitazone was devoid of genotoxic potential in a comprehensive battery of *in vivo* and *in vitro* genotoxicity assays. An increased incidence of hyperplasia (males and females) and tumours (males) of the urinary bladder epithelium was apparent in rats treated with pioglitazone for up to 2 years.

The formation and presence of urinary calculi with subsequent irritation and hyperplasia was postulated as the mechanistic basis for the observed tumourigenic response in the male rat. A

24-month mechanistic study in male rats demonstrated that administration of pioglitazone resulted in an increased incidence of hyperplastic changes in the bladder. Dietary acidification significantly decreased but did not abolish the incidence of tumours. The presence of microcrystals exacerbated the hyperplastic response but was not considered to be the primary cause of hyperplastic changes. The relevance to humans of the tumourigenic findings in the male rat cannot be excluded.

There was no tumorigenic response in mice of either sex. Hyperplasia of the urinary bladder was not seen in dogs or monkeys treated with pioglitazone for up to 12 months.

In an animal model of familial adenomatous polyposis (FAP), treatment with two other thiazolidinediones increased tumour multiplicity in the colon. The relevance of this finding is unknown.

Glimepiride

Preclinical effects observed occurred at exposures sufficiently in excess of the maximum human exposure as to indicate little relevance to clinical use, or were due to the pharmacodynamic action (hypoglycaemia) of the compound. This finding is based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproduction toxicity studies. In the latter (covering embryotoxicity, teratogenicity and developmental toxicity), undesirable effects observed were considered to be secondary to the hypoglycaemic effects induced by the compound in dams and in offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline
Croscarmellose sodium
Hydroxypropylcellulose
Lactose monohydrate
Magnesium stearate
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blisters; packs of 14, 28, 30, 50, 90 or 98 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Takeda Global Research and Development Centre (Europe) Ltd
61 Aldwych
London
WC2B 4AE
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/06/366/005-10

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th January 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Tandemact 45 mg/4 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 45 mg of pioglitazone (as hydrochloride) and 4 mg of glimepiride.

Excipient: Each tablet contains approximately 214 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White to off-white, round, flat and embossed '4833 G' on one face and '45/4' on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tandemact is indicated as second line 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.

After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained (see section 4.4).

4.2 Posology and method of administration

If patients report hypoglycaemia, the dose of Tandemact should be reduced or free combination therapy should be considered.

If patients are receiving pioglitazone in combination with a sulphonylurea other than glimepiride, patients should be stabilised with concomitant pioglitazone and glimepiride before switching to Tandemact.

Elderly:

No dosage adjustment is necessary for elderly patients (see section 5.2). Physicians should start treatment with the lowest available dose and increase the dose gradually, particularly when pioglitazone is used in combination with insulin (see section 4.4 Fluid retention and cardiac failure).

Patients with renal impairment:

Tandemact should not be used in patients with severe renal function disorders (creatinine clearance <30 ml/min, see section 4.3).

Patients with hepatic impairment:

Tandemact should not be used in patients with hepatic impairment (see section 4.3).

Children and adolescents:

Tandemact is not recommended for use in patients below age 18 due to insufficient data on safety and efficacy.

The tablets are taken orally once daily shortly before or with the first main meal. The tablets should be swallowed whole with some liquid.

4.3 Contraindications

Tandemact is contraindicated in patients with:

- Hypersensitivity to the active substances, or to any of the excipients, or other sulphonylureas or sulphonamides
- Cardiac failure or history of cardiac failure (NYHA stages I to IV)
- Current bladder cancer or a history of bladder cancer
- Uninvestigated macroscopic haematuria
- Hepatic impairment
- Type 1 diabetes mellitus
- Diabetic coma
- Diabetic ketoacidosis
- Severe renal function disorders
- Pregnancy
- Lactation

4.4 Special warnings and precautions for use

There is no clinical trial experience of other oral anti-hyperglycaemic agents added to treatment with Tandemact or concomitantly administered glimepiride and pioglitazone.

Hypoglycaemia:

When meals are taken at irregular hours or skipped altogether, treatment with Tandemact may lead to hypoglycaemia due to the sulphonylurea component. Symptoms can almost always be promptly controlled by immediate intake of carbohydrates (sugar). Artificial sweeteners have no effect.

It is known from other sulphonylureas that, despite initially successful countermeasures, hypoglycaemia may recur. Severe hypoglycaemia or prolonged hypoglycaemia, only temporarily controlled by the usual amounts of sugar, require immediate medical treatment and occasionally hospitalisation.

Treatment with Tandemact requires regular monitoring of glycaemic control.

Fluid retention and cardiac failure:

Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction or symptomatic coronary artery disease or the elderly), physicians should start with the lowest available dose of pioglitazone and increase the dose gradually. Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with reduced cardiac reserve.

There have been cases of cardiac failure reported from the market when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure. Since insulin and pioglitazone are both associated with fluid retention, concomitant administration may increase the risk of oedema. Tandemact should be discontinued if any deterioration in cardiac state occurs.

A cardiovascular outcome study of pioglitazone has been performed in patients under 75 years with type 2 diabetes mellitus and pre-existing major macrovascular disease. Pioglitazone or placebo was added to existing antidiabetic and cardiovascular therapy for up to 3.5 years. This study showed an increase in reports of heart failure, however this did not lead to an increase in mortality in this study.

Elderly:

Combination use with insulin should be considered with caution in the elderly because of increased risk of serious heart failure.

In light of age- related risks (especially bladder cancer, fractures and heart failure), the balance of benefits and risks should be considered carefully both before and during treatment in the elderly.

Bladder cancer:

Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12506 patients, 0.15%) than in control groups (7 cases from 10212 patients, 0.07%) HR=2.64 (95% CI 1.11-6.31, P=0.029). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Available epidemiological data also suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone in particular in patients treated for the longest durations and with the highest cumulative doses. A possible risk after short term treatment cannot be excluded.

Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic haematuria should be investigated before starting pioglitazone therapy.

Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

Liver function:

There have been rare reports of hepatocellular dysfunction during post-marketing experience with pioglitazone and glimepiride (see section 4.8). It is recommended, therefore, that patients treated with Tandemact undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with Tandemact in all patients. Therapy with Tandemact should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 X upper limit of normal) or with any other evidence of liver disease.
Following initiation of therapy with Tandemact, it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3 X upper limit of normal during Tandemact therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with Tandemact should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, therapy with Tandemact should be discontinued.

Weight gain:

In clinical trials with pioglitazone and sulphonylurea monotherapy or in combination there was evidence of dose related weight gain, which may be due to fat accumulation and in some cases associated with fluid retention. In some cases weight increase may be a symptom of cardiac failure, therefore weight should be closely monitored. Part of the treatment of diabetes is dietary control. Patients should be advised to adhere strictly to a calorie-controlled diet.

Haematology:

Rare changes in haematology have been observed with glimepiride treatment (see section 4.8). Treatment with Tandemact therefore requires regular haematological monitoring (especially leucocytes and platelets).

During therapy with pioglitazone there was a small reduction in mean haemoglobin (4 % relative reduction) and haematocrit (4.1 % relative reduction), consistent with haemodilution. Similar changes were seen in metformin (haemoglobin 3 - 4 % and haematocrit 3.6 - 4.1 % relative reductions) and to a lesser extent sulphonylurea and insulin (haemoglobin 1 - 2 % and haematocrit 1 - 3.2 % relative reductions) treated patients in comparative controlled trials with pioglitazone.

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since glimepiride belongs to the chemical class of sulfonylurea medicinal products, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

Eye disorders:

Post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with thiazolidinediones, including pioglitazone. Many of these patients reported concurrent peripheral oedema. It is unclear whether or not there is a direct association between pioglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity; an appropriate ophthalmological referral should be considered.

Others:

An increased incidence in bone fractures in women was seen in a pooled analysis of adverse event reports of bone fracture from randomised, controlled, double blind clinical trials in over 8100 pioglitazone and 7400 comparator treated patients, on treatment for up to 3.5 years.

Fractures were observed in 2.6% of women taking pioglitazone compared to 1.7% of women treated with a comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).

The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this dataset on pioglitazone is therefore 0.8 fractures per 100 patient years of use.

In the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%; 1.0 fractures per 100 patient years) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures per 100 patient years) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).

The risk of fractures should be considered in the long term care of women treated with pioglitazone.

As a consequence of enhancing insulin action, pioglitazone treatment in patients with polycystic ovarian syndrome may result in resumption of ovulation. These patients may be at risk of pregnancy.

Patients should be aware of the risk of pregnancy and if a patient wishes to become pregnant or if pregnancy occurs, the treatment should be discontinued (see section 4.6).

Pioglitazone should be used with caution during concomitant administration of cytochrome P450 2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin). Glycaemic control should be monitored closely. Pioglitazone dose adjustment within the recommended posology or changes in diabetic treatment should be considered (see section 4.5).

The tablets contain lactose monohydrate and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for Tandemact, however, the concomitant use of the active substances in patients in clinical use has not resulted in any unexpected interactions. The following statements reflect the information available on the individual active substances (pioglitazone and glimepiride).

Pioglitazone

Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Co-administration of pioglitazone with sulphonylureas does not appear to affect the pharmacokinetics of the sulphonylurea. Studies in man suggest no induction of the main inducible cytochrome P450, 1A, 2C8/9 and 3A4. *In vitro* studies have shown no inhibition of any subtype of cytochrome P450. Interactions with substances metabolised by these enzymes, e.g. oral contraceptives, cyclosporin, calcium channel blockers, and HMGCoA reductase inhibitors are not to be expected.

Co-administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) is reported to result in a 3-fold increase in AUC of pioglitazone. A decrease in the dose of pioglitazone may be needed when gemfibrozil is concomitantly administered. Close monitoring of glycaemic control should be considered (see section 4.4)**.** Co-administration of pioglitazone with rifampicin (an inducer of cytochrome P450 2C8) is reported to result in a 54% decrease in AUC of pioglitazone. The pioglitazone dose may need to be increased when rifampicin is concomitantly administered. Close monitoring of glycaemic control should be considered (see section 4.4).

Glimepiride

If glimepiride is taken simultaneously with certain other medicinal products, both undesired increases and decreases in the hypoglycaemic action of glimepiride can occur. For this reason, other medicinal products should only be taken with Tandemact with the knowledge (or at the prescription) of the doctor.

Based on the experience with glimepiride and with other sulphonylurea the following interactions have to be mentioned.

Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following active substances is taken, for example:
phenylbutazone, azapropazon and oxyfenbutazone
insulin and oral antidiabetic products
metformin
salicylates and p-amino-salicylic acid
anabolic steroids and male sex hormones
chloramphenicol
coumarin anticoagulants
fenfluramine

fibrates
ACE inhibitors
fluoxetine
allopurinol
sympatholytics
cyclo-, tro-and iphosphamides
sulphinpyrazone
certain long-acting sulphonamides
tetracyclines
MAO-inhibitors
quinolone antibiotics
probenecid
miconazol
pentoxyfylline (high dose parenteral)
tritoqualine
fluconazole

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following active substances is taken, for example:

oestrogens and progestagens,
saluretics, thiazide diuretics,
thyroid stimulating agents, glucocorticoids,
phenothiazine derivatives, chlorpromazine,
adrenaline and sympathicomimetics,
nicotinic acid (high dosages) and nicotinic acid derivatives,
laxatives (long-term use),
phenytoin, diazoxide,
glucagon, barbiturates and rifampicin.
acetozolamide

H_2 antagonists, betablockers, clonidine and reserpine may lead to either potentiation or weakening of the blood glucose lowering effect.

Under the influence of sympatholytic active substances such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counterregulation to hypoglycaemia may be reduced or absent.

Alcohol intake may potentiate or weaken the hypoglycaemic action of glimepiride in an unpredictable fashion.

Glimepiride may either potentiate or weaken the effects of coumarin derivatives.

4.6 Pregnancy and lactation

There are no adequate data from the use of pioglitazone and glimepiride in pregnant women. Studies of pioglitazone in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. There are no adequate data from the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which was most likely related to the pharmacological action (hypoglycaemia) of glimepiride. Tandemact must not be used during pregnancy.

Sulphonylurea-derivatives like glimepiride pass into the breast milk. Pioglitazone has been shown to be present in the milk of lactating rats. It is not known whether pioglitazone is secreted in human milk. Therefore, Tandemact must not be administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia from glimepiride or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warnings of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machines in these circumstances.

4.8 Undesirable effects

No therapeutic clinical trials have been conducted with Tandemact. However, bioequivalence of Tandemact with coadministered pioglitazone and glimepiride has been demonstrated (see section 5.2).

Adverse reactions reported in excess (> 0.5 %) of placebo and as more than an isolated case in patients receiving pioglitazone in double-blind studies in combination with a sulphonylurea, including glimepiride, are listed below as MedDRA preferred term by system organ class and absolute frequency. Frequencies are defined as: common > 1/100, < 1/10; uncommon > 1/1000, < 1/100; rare > 1/10000, < 1/1000; very rare < 1/10000; isolated reports: not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

PIOGLITAZONE IN COMBINATION THERAPY WITH SULPHONYLUREA

Ear and labyrinth disorders

Uncommon: vertigo

Eye disorders

Uncommon: visual disturbance

Gastrointestinal disorders

Common: flatulence

General disorders and administration site conditions

Uncommon: fatigue

Investigations

Common: weight increased

Uncommon: increased lactic dehydrogenase

Metabolism and nutritional disorders

Uncommon: hypoglycaemia, appetite increased

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Uncommon: bladder cancer

Nervous system disorders

Common: dizziness

Uncommon: headache

Renal and urinary disorders

Uncommon: glycosuria, proteinuria

Skin and subcutaneous tissue disorders

Uncommon: sweating

Oedema was reported in 6 - 9 % of patients treated with pioglitazone over one year in controlled clinical trials. The oedema rates for comparator groups (sulphonylurea, metformin) were 2 - 5 %. The reports of oedema were generally mild to moderate and usually did not require discontinuation of treatment.

In active comparator controlled trials mean weight increase with pioglitazone given as monotherapy was 2 - 3 kg over one year. This is similar to that seen in a sulphonylurea active comparator group. In combination trials pioglitazone added to a sulphonylurea resulted in a mean weight increase over one year of 2.8 kg.

Visual disturbance has been reported mainly early in treatment and is related to changes in blood glucose due to temporary alteration in the turgidity and refractive index of the lens as seen with other hypoglycaemic agents.

In clinical trials with pioglitazone the incidence of elevations of ALT greater than three times the upper limit of normal was equal to placebo but less than that seen in metformin or sulphonylurea comparator groups. Mean levels of liver enzymes decreased with treatment with pioglitazone. Rare cases of elevated liver enzymes and hepatocellular dysfunction have occurred in post-marketing experience. Although in very rare cases fatal outcome has been reported, causal relationship has not been established.

In controlled clinical trials the incidence of reports of heart failure with pioglitazone treatment was the same as in placebo, metformin and sulphonylurea treatment groups, but was increased when used in combination therapy with insulin. In an outcome study of patients with pre-existing major macrovascular disease, the incidence of serious heart failure was 1.6% higher with pioglitazone than with placebo, when added to therapy that included in insulin. However, this did not lead to an increase in mortality in this study. Heart failure has been reported rarely with marketing use of pioglitazone, but more frequently when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure.

Additional information on the individual active substances of the fixed dose combination

Pioglitazone

In double blind placebo controlled clinical trials with pioglitazone upper respiratory tract infection and hypoaesthesia were common; sinusitis and insomnia were uncommon.

In controlled clinical trials the incidence of reports of heart failure with pioglitazone treatment was the same as in placebo, metformin and sulphonylurea treatment groups. Heart failure has been reported rarely with marketing use of pioglitazone.

POST MARKETING DATA

Eye disorders

Macular oedema: not known

Glimepiride

Based on experience with glimepiride and with other sulphonylureas the following adverse reactions have to be mentioned.

Immune system disorders

Very rare: Allergic shock, allergic vasculitis

Blood and lymphatic system disorders

Rare: Changes in haematology

Gastro-intestinal disorders

Very rare: Vomiting, diarrhoea, nausea, abdominal pressure, feeling of fullness in the stomach, abdominal pain

Hepato-biliary disorders

Very rare: Hepatitis, impairment of liver function (with cholestasis and jaundice)

Skin and subcutaneous tissue disorders

Very rare: Hypersensitivity to light

Investigations

Very rare: Decrease in sodium serum concentrations

In very rare cases mild hypersensivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock. Hypersensitivity reactions of the skin may occur as itching, rash, and urticaria. Cross allergenicity with sulphonylureas, sulphonamides or related substances is possible.

Moderate to severe thrombocytopenia, leucopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anemia and pancyto-penia may occur. These are in general reversible upon discontinuation of medication.

Gastro-intestinal complaints are very rare and seldom lead to discontinuation of therapy.

Elevation of liver enzymes may occur. In very rare cases, impairment of liver function (e.g. with cholestasis and jaundice) may develop, as well as hepatitis which may progress to liver failure.

A pooled analysis was conducted of adverse event reports of bone fractures from randomised, comparator controlled, double blind clinical trials in over 8100 patients in the pioglitazone-treated groups and 7400 in the comparator-treated groups of up to 3.5 years duration. A higher rate of fractures was observed in women taking pioglitazone (2.6%) versus comparator (1.7%). No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).

In the 3.5 year PROactive study, 44/870 (5.1%) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).

4.9 Overdose

No case of overdose has been reported.

Patients have taken pioglitazone at higher than the recommended highest dose of 45 mg daily. The maximum reported dose of 120 mg/day for four days, then 180 mg/day for seven days was not associated with any symptoms.

After ingestion of an overdosage of glimepiride, hypoglycaemia may occur, lasting from 12 to 72 hours, and may recur after initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general observation in hospital is recommended. Nausea, vomiting and epigastric pain may occur. The hypoglycaemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, coordination problems, sleepiness, coma and convulsions.

Treatment of overdosage of Tandemact primarily consists of preventing absorption of glimepiride by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium-sulphate (laxative). If large quantities have been ingested, gastric lavage is indicated, followed by activated charcoal and sodium-sulphate. In case of (severe) overdosage hospitalization in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary by a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic.

In particular when treating hypoglycaemia due to accidental intake of Tandemact in infants and young children, the dose of glucose given must be carefully controlled to avoid the possibility of producing dangerous hyperglycaemia. Blood glucose should be closely monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of oral blood glucose lowering drugs; ATC code: A10BD06.

Tandemact combines two antihyperglycaemic agents with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: pioglitazone, a member of the thiazolidinedione class and glimepiride, a member of the sulphonylurea class. Thiazolidinediones act primarily by reducing insulin resistance and sulphonylureas primarily by inducing insulin release from pancreatic beta cells.

<u>Pioglitazone</u>

Pioglitazone effects may be mediated by a reduction of insulin resistance. Pioglitazone appears to act via activation of specific nuclear receptors (peroxisome proliferator activated receptor gamma) leading to increased insulin sensitivity of liver, fat and skeletal muscle cells in animals. Treatment with pioglitazone has been shown to reduce hepatic glucose output and to increase peripheral glucose disposal in the case of insulin resistance.

Fasting and postprandial glycaemic control is improved in patients with type 2 diabetes mellitus. The improved glycaemic control is associated with a reduction in both fasting and postprandial plasma insulin concentrations. A clinical trial of pioglitazone vs. gliclazide as monotherapy was extended to two years in order to assess time to treatment failure (defined as appearance of $HbA_{1c} \geq 8.0$ % after the first six months of therapy). Kaplan-Meier analysis showed shorter time to treatment failure in

patients treated with gliclazide, compared with pioglitazone. At two years, glycaemic control (defined as HbA_{1c} < 8.0 %) was sustained in 69 % of patients treated with pioglitazone, compared with 50 % of patients on gliclazide. In a two-year study of combination therapy comparing pioglitazone with gliclazide when added to metformin, glycaemic control measured as mean change from baseline in HbA_{1c} was similar between treatment groups after one year. The rate of deterioration of HbA_{1c} during the second year was less with pioglitazone than with gliclazide.

In a placebo controlled trial, patients with inadequate glycaemic control despite a three month insulin optimisation period were randomised to pioglitazone or placebo for 12 months. Patients receiving pioglitazone had a mean reduction in HbA_{1c} of 0.45% compared with those continuing on insulin alone, and a reduction of insulin dose in the pioglitazone treated group.

HOMA analysis shows that pioglitazone improves beta cell function as well as increasing insulin sensitivity. Two-year clinical studies have shown maintenance of this effect.

In one year clinical trials, pioglitazone consistently gave a statistically significant reduction in the albumin/creatinine ratio compared to baseline.

The effect of pioglitazone (45 mg monotherapy *vs.* placebo) was studied in a small 18-week trial in type 2 diabetics. Pioglitazone was associated with significant weight gain. Visceral fat was significantly decreased, while there was an increase in extra-abdominal fat mass. Similar changes in body fat distribution on pioglitazone have been accompanied by an improvement in insulin sensitivity. In most clinical trials, reduced total plasma triglycerides and free fatty acids, and increased HDL-cholesterol levels were observed as compared to placebo, with small, but not clinically significant increases in LDL-cholesterol levels. In clinical trials of up to two years duration, pioglitazone reduced total plasma triglycerides and free fatty acids, and increased HDL cholesterol levels, compared with placebo, metformin or gliclazide. Pioglitazone did not cause statistically significant increases in LDL cholesterol levels compared with placebo, whilst reductions were observed with metformin and gliclazide. In a 20-week study, as well as reducing fasting triglycerides, pioglitazone reduced post prandial hypertriglyceridaemia through an effect on both absorbed and hepatically synthesised triglycerides. These effects were independent of pioglitazone's effects on glycaemia and were statistically significant different to glibenclamide.

In PROactive, a cardiovascular outcome study, 5238 patients with type 2 diabetes mellitus and pre-existing major macrovascular disease were randomised to pioglitazone or placebo in addition to existing antidiabetic and cardiovascular therapy, for up to 3.5 years. The study population had an average age of 62 years; the average duration of diabetes was 9.5 years. Approximately one third of patients were receiving insulin in combination with metformin and/or a sulphonylurea. To be eligible patients had to have had one or more of the following: myocardial infarction, stroke, percutaneous cardiac intervention or coronary artery bypass graft, acute coronary syndrome, coronary artery disease, or peripheral arterial obstructive disease. Almost half of the patients had a previous myocardial infarction and approximately 20% had had a stroke. Approximately half of the study population had at least two of the cardiovascular history entry criteria. Almost all subjects (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors, angiotensin II antagonists, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates).

Although the study failed regarding its primary endpoint, which was a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, major leg amputation, coronary revascularisation and leg revascularisation, the results suggest that there are no long-term cardiovascular concerns regarding use of pioglitazone. However, the incidence of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.

Glimepiride

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells.

As with other sulphonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulphonylureas.

Insulin release:

Sulphonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarisation of the beta cell and results – by opening of calcium channels – in an increased influx of calcium into the cell. This leads to insulin release through exocytosis. Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel but which is different from the usual sulphonylurea binding site.

Extrapancreatic activity:

The extrapancreatic effects are for example an improvement of the sensitivity of the peripheral tissue for insulin and a decrease of the insulin uptake by the liver.

The uptake of glucose from blood into peripheral muscle and fat tissues occurs via a special transport proteins, located in the cells membrane. The transport of glucose in these tissues is the rate limiting step in the use of glucose. Glimepiride increases very rapidly the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulated glucose uptake. Glimepiride increases the activity of the glycosyl-phosphatidylinositol-specific phospholipase C which may be correlated with the induced lipogenesis and glycogenesis in isolated fat and muscle cells. Glimepiride inhibits the glucose production in the liver by increasing the intracellular concentration of fructose-2,6-bisphosphate, which in turn inhibits the gluconeogenesis.

General:

In healthy persons, the minimum effective oral dose is approximately 0.6 mg. The effect of glimepiride is dose-dependent and reproducible. The physiological response to acute physical exercise, reduction of insulin secretion, is still present under glimepiride.

There was no significant difference in effect regardless of whether glimepiride was given 30 minutes or immediately before a meal. In diabetic patients, good metabolic control over 24 hours can be achieved with a single daily dose.

Although the hydroxy metabolite of glimepiride caused a small but significant decrease in serum glucose in healthy persons, it accounts for only a minor part of the total effect.

5.2 Pharmacokinetic properties

Tandemact

Studies in human volunteers have shown Tandemact to be bioequivalent to the administration of pioglitazone and glimepiride given as separate tablets.

The following statements reflect the pharmacokinetic properties of the individual active substances of Tandemact

Pioglitazone

Absorption:

Following oral administration, pioglitazone is rapidly absorbed, and peak plasma concentrations of unchanged pioglitazone are usually achieved 2 hours after administration. Proportional increases of the plasma concentration were observed for doses from 2 - 60 mg. Steady state is achieved after

4-7 days of dosing. Repeated dosing does not result in accumulation of the compound or metabolites. Absorption is not influenced by food intake. Absolute bioavailability is greater than 80 %.

Distribution:

The estimated volume of distribution in humans is 0.25 l/kg.

Pioglitazone and all active metabolites are extensively bound to plasma protein (> 99 %).

Metabolism:

Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 although other isoforms may be involved to a lesser degree. Three of the six identified metabolites are active (M-II, M-III, and M-IV). When activity, concentrations and protein binding are taken into account, pioglitazone and metabolite M-III contribute equally to efficacy. On this basis M-IV contribution to efficacy is approximately three-fold that of pioglitazone, whilst the relative efficacy of M-II is minimal.

In vitro studies have shown no evidence that pioglitazone inhibits any subtype of cytochrome P450. There is no induction of the main inducible P450 isoenzymes 1A, 2C8/9, and 3A4 in man.

Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Concomitant administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) or with rifampicin (an inducer of cytochrome P450 2C8) is reported to increase or decrease, respectively, the plasma concentration of pioglitazone (see section 4.5).

Elimination:

Following oral administration of radiolabelled pioglitazone to man, recovered label was mainly in faeces (55%) and a lesser amount in urine (45 %). In animals, only a small amount of unchanged pioglitazone can be detected in either urine or faeces. The mean plasma elimination half-life of unchanged pioglitazone in man is 5 to 6 hours and for its total active metabolites 16 to 23 hours.

Elderly:

Steady state pharmacokinetics are similar in patients age 65 and over and young subjects.

Patients with renal impairment:

In patients with renal impairment, plasma concentrations of pioglitazone and its metabolites are lower than those seen in subjects with normal renal function, but oral clearance of parent substance is similar. Thus free (unbound) pioglitazone concentration is unchanged.

Patients with hepatic impairment:

Total plasma concentration of pioglitazone is unchanged, but with an increased volume of distribution. Intrinsic clearance is therefore reduced, coupled with a higher unbound fraction of pioglitazone.

Glimepiride

Absorption:

The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations (C_{max}) are reached approximately 2.5 hours after oral intake (mean 0.3 µg/ml during multiple dosing

of 4 mg daily) and there is a linear relationship between dose and both C_{max} and AUC (area under the time/concentration curve).

Distribution:

Glimepiride has a very low distribution volume (approximately 8.8 litres) which is roughly equal to the albumin distribution space, high protein binding (> 99%), and a low clearance (approximately 48 ml/min).

In animals, glimepiride is excreted in milk. Glimepiride is transferred to the placenta. Passage of the blood brain barrier is low.

Biotransformation and elimination:

Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted.

After a single dose of radiolabelled glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites – most probably resulting from hepatic metabolism (major enzyme is CYP2C9) – were identified both in urine and faeces: the hydroxy derivative and the carboxy derivative. After oral administration of glimepiride, the terminal half-lives of those metabolites were 3 to 6 and 5 to 6 hours respectively.

Comparison of single and multiple once-daily dosing revealed no significant differences in pharmacokinetics, and the intra-individual variability was very low. There was no relevant accumulation.

Pharmacokinetics were similar in males and females, as well as in young and elderly (above 65 years) patients. In patients with low creatinine clearance, there was a tendency for glimepiride clearance to increase and for average serum concentrations to decrease, most probably resulting from a more rapid elimination because of lower protein binding. Renal elimination of the two metabolites was impaired. Overall no additional risk of accumulation is to be assumed in such patients.

Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

5.3 Preclinical safety data

No animal studies have been conducted with the combined products of Tandemact. The following data are findings in studies performed with pioglitazone or glimepiride individually.

Pioglitazone

In toxicology studies, plasma volume expansion with haemodilution, anaemia, and reversible eccentric cardiac hypertrophy was consistently apparent after repeated dosing of mice, rats, dogs, and monkeys. In addition, increased fatty deposition and infiltration were observed. These findings were observed across species at plasma concentrations ≤ 4 times the clinical exposure. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth.

Pioglitazone was devoid of genotoxic potential in a comprehensive battery of *in vivo* and *in vitro* genotoxicity assays. An increased incidence of hyperplasia (males and females) and tumours (males) of the urinary bladder epithelium was apparent in rats treated with pioglitazone for up to 2 years.

The formation and presence of urinary calculi with subsequent irritation and hyperplasia was postulated as the mechanistic basis for the observed tumourigenic response in the male rat. A

24-month mechanistic study in male rats demonstrated that administration of pioglitazone resulted in an increased incidence of hyperplastic changes in the bladder. Dietary acidification significantly decreased but did not abolish the incidence of tumours. The presence of microcrystals exacerbated the hyperplastic response but was not considered to be the primary cause of hyperplastic changes. The relevance to humans of the tumourigenic findings in the male rat cannot be excluded.

There was no tumorigenic response in mice of either sex. Hyperplasia of the urinary bladder was not seen in dogs or monkeys treated with pioglitazone for up to 12 months.

In an animal model of familial adenomatous polyposis (FAP), treatment with two other thiazolidinediones increased tumour multiplicity in the colon. The relevance of this finding is unknown.

Glimepiride

Preclinical effects observed occurred at exposures sufficiently in excess of the maximum human exposure as to indicate little relevance to clinical use, or were due to the pharmacodynamic action (hypoglycaemia) of the compound. This finding is based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproduction toxicity studies. In the latter (covering embryotoxicity, teratogenicity and developmental toxicity), undesirable effects observed were considered to be secondary to the hypoglycaemic effects induced by the compound in dams and in offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline
Croscarmellose sodium
Hydroxypropylcellulose
Lactose monohydrate
Magnesium stearate
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blisters; packs of 14, 28, 30, 50, 90 or 98 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Takeda Global Research and Development Centre (Europe) Ltd
61 Aldwych
London
WC2B 4AE
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/06/366/011-016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th January 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Takeda Ireland Limited
Bray Business Park
Kilruddery
County Wicklow
Ireland

Takeda Italia Farmaceutici S.p.A
Via Crosa 86,
28065 Cerano (NO)
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH shall submit within 1 month of the Commission decision an updated Risk Management Plan which shall include a risk minimisation plan which includes additional risk minimisation measures to address the identified risks of bladder cancer and heart failure, as detailed below.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

PSURs

The PSUR cycle for the medicinal product should follow a half-yearly cycle until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

The MAH shall provide an educational pack targeting all physicians who are expected to prescribe/use Pioglitazone. Prior to distribution of the prescriber guide in each Member State, the MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority.

- This educational pack is aimed at strengthening awareness of important identified risks of bladder cancer and heart failure and the overall recommendations intended to optimise the benefit-risk margin at the patient level.
- The physician educational pack should contain: The Summary of Product Characteristics, package leaflet, and a Prescriber Guide.

The Prescriber Guide should highlight the following:
- Patient selection criteria including that Pioglitazone should not be used as first line therapy and emphasising the need for regular review of treatment benefit.
- The risk of bladder cancer and relevant risk minimisation advice.
- The risk of heart failure and relevant risk minimisation advice.
- Caution in use in the elderly in light of age related risks (in particular bladder cancer, fractures and heart failure).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tandemact 30 mg/2 mg tablets

Pioglitazone/Glimepiride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 30 mg of pioglitazone (as hydrochloride) and 2 mg of glimepiride.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28tablets
30 tablets
50 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry date:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Global Research and Development Centre (Europe) Ltd
61 Aldwych
London
WC2B 4AE
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/366/017 14 tablets
EU/1/06/366/018 28 tablets
EU/1/06/366/019 30 tablets
EU/1/06/366/020 50 tablets
EU/1/06/366/021 90 tablets
EU/1/06/366/022 98 tablets

13. BATCH NUMBER

Batch number: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tandemact 30 mg/2 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tandemact 30 mg/4 mg tablets

Pioglitazone/Glimepiride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 30 mg of pioglitazone (as hydrochloride) and 4 mg of glimepiride.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28tablets
30 tablets
50 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry date:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Global Research and Development Centre (Europe) Ltd
61 Aldwych
London
WC2B 4AE
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/366/005 14 tablets
EU/1/06/366/006 28 tablets
EU/1/06/366/007 30 tablets
EU/1/06/366/008 50 tablets
EU/1/06/366/009 90 tablets
EU/1/06/366/010 98 tablets

13. BATCH NUMBER

Batch number: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tandemact 30 mg/4 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tandemact 45 mg/4 mg tablets

Pioglitazone/Glimepiride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 45 mg of pioglitazone (as hydrochloride) and 4 mg of glimepiride.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28 tablets
30 tablets
50 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry date:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Global Research and Development Centre (Europe) Ltd
61 Aldwych
London
WC2B 4AE
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/366/011 14 tablets
EU/1/06/366/012 28 tablets
EU/1/06/366/013 30 tablets
EU/1/06/366/014 50 tablets
EU/1/06/366/015 90 tablets
EU/1/06/366/016 98 tablets

13. BATCH NUMBER

Batch number: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tandemact 45 mg/4 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Tandemact 30 mg/2 mg tablets

Pioglitazone/Glimepiride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda (logo)

3. EXPIRY DATE

Expiry date:

4. BATCH NUMBER

Batch number:

5. OTHER (FOR CALENDARISED PACKS)

MON
TUE
WED
THU
FRI
SAT
SUN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Tandemact 30 mg/4 mg tablets

Pioglitazone/Glimepiride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda (logo)

3. EXPIRY DATE

Expiry date:

4. BATCH NUMBER

Batch number:

5. OTHER (FOR CALENDARISED PACKS)

MON
TUE
WED
THU
FRI
SAT
SUN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Tandemact 45 mg/4 mg tablets

Pioglitazone/Glimepiride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda (logo)

3. EXPIRY DATE

Expiry date:

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5. OTHER (FOR CALENDARISED PACKS)

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B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
Tandemact 30 mg/2 mg tablets

Pioglitazone /glimepiride

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT TANDEMACT IS AND WHAT IT IS USED FOR

Tandemact is used when metformin is not suitable for the treatment of type 2 (non-insulin dependent) diabetes mellitus. This is the diabetes that usually develops in adulthood.

Tandemact helps control the level of sugar in your blood when you have type 2 diabetes by increasing the amount of insulin available and helping your body make better use of it. Your doctor will check whether Tandemact is working 3 to 6 months after you start taking it.

2. BEFORE YOU TAKE TANDEMACT

Do not take Tandemact:

- If you are allergic (hypersensitive) to pioglitazone, glimepiride, other sulphonylureas or sulphonamides, or any of the other ingredients of Tandemact.
- If you have heart failure.
- If you have liver disease.
- If you have severe problems with your kidneys.
- If you have or have ever had bladder cancer.
- If you have blood in your urine that your doctor has not checked.
- If you have insulin dependent diabetes (Type 1).
- If you are pregnant.
- If you are breast-feeding.

Take special care with Tandemact:

Tell your doctor before you start to take this medicine:
- If you are planning to become pregnant.
- If you have polycystic ovary syndrome. There may be an increased possibility of your becoming pregnant because of how your medicine works.
- If you have a problem with your liver or heart.
- If you have a special type of diabetic eye disease called macular oedema (swelling of the back of the eye).

- If you are already taking other medicines for the treatment of diabetes.
- If you are under 18 years of age because use in such patients is not recommended.

Taking other medicines:

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because some medicines can weaken or strengthen the effect of Tandemact on the level of sugar in your blood.

Pregnancy and breast-feeding:

Do not take Tandemact if you are pregnant or breast-feeding. Tell your doctor if you are, you think you might be or are planning to become pregnant, or if you are planning to breast-feed your baby.

Driving and using machines:

Alertness and reaction time may be impaired due to low or high blood sugar due to glimepiride, especially when beginning or after altering treatment or when Tandemact is not taken regularly. This may affect your ability to drive or operate machinery.

Important information about some of the ingredients of Tandemact:

This medicinal product contains lactose monohydrate. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking Tandemact.

3. HOW TO TAKE TANDEMACT

Always take Tandemact exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is one tablet taken once daily shortly before or with the first main meal. Tablets should be swallowed whole with some liquid. If necessary your doctor may tell you to take a different dose.

If you have the impression that the effect of Tandemact is too weak, talk to your doctor.

If you are following a special diet for diabetes, you should continue with this while you are taking Tandemact.

Your weight should be checked at regular intervals; if your weight increases, inform your doctor.

In clinical trials in which pioglitazone was compared to other oral anti diabetic medicines or placebo (dummy pill), a higher number of bone fractures was seen in women (but not in men) taking pioglitazone. Your doctor will take this into account when treating your diabetes.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Your doctor will ask you to have blood tests periodically during treatment with Tandemact.

If you take more Tandemact than you should:

If you accidentally take too many tablets, or if someone else or a child takes your medicine, talk to a doctor or pharmacist immediately.

If you forget to take Tandemact:

Try to take Tandemact daily as prescribed. However if you miss a dose, just carry on with the next dose as normal. Do not take an extra tablet to make up for the one you missed.

If you stop taking Tandemact:

Do not stop taking Tandemact without first discussing it with your doctor or pharmacist.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Tandemact can cause side effects, although not everybody gets them.

Bladder cancer has been experienced uncommonly (1 to 10 users in 1000) in patients taking Tandemact. Signs and symptoms include blood in your urine, pain when urinating or a sudden need to urinate. If you experience any of these, talk to your doctor as soon as possible.

Some patients experienced the following side effects whilst taking pioglitazone and sulphonylureas, including glimepiride:

Common: affects 1 to 10 users in 100 patients
- weight gain
- dizziness
- flatulence
- localised swelling (oedema)
- cold or runny nose
- numbness

Uncommon: affects 1 to 10 users in 1,000 patients
- bladder cancer
- headache
- sinusitis
- vertigo
- abnormal vision
- sweating
- tiredness
- sleeplessness
- decreased blood sugar
- sugar in urine
- proteins in urine
- increased appetite

Rare: affects 1 to 10 users in 10,000 patients
noticeable changes in blood
risk of bone fracture
risk of heart failure

Very Rare: affects less than 1 user in 10,000 patients
- liver disease
- allergic reactions including allergic shock
- nausea, vomiting and diarrhoea
- abdominal pain
- abdominal pressure
- feeling of fullness in the stomach
- decrease in the number of blood cells known as platelets

- sensitivity to light
- decrease in sodium concentrations in the blood

Blurred vision due to swelling (or fluid) in the back of the eye has been reported. If you experience these symptoms for the first time or if they get worse talk to your doctor as soon as possible. It is important to know what symptoms to expect when hypoglycaemia (low blood sugar) occurs. Ask your doctor or pharmacist for more information if you are not sure how to recognise this. The symptoms may include cold sweat, tiredness, headache, rapid heartbeat, hunger pangs, irritability, nervousness or nausea. Tell your doctor if you notice such symptoms.

Lowering of the Hb level and breakdown of red blood cells (haemolytic anemia) can occur in patients missing the enzyme Glucose-6-phosphodehydrogenase.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. STORING TANDEMACT

Keep out of the reach and sight of children.

Do not use Tandemact after the expiry date which is stated on the carton and blister.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via waste water or household waste. Ask you pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Tandemact contains:

The active substances are pioglitazone and glimepiride. Each tablet contains 30 mg pioglitazone (as hydrochloride) and 2 mg glimepiride. The other ingredients are cellulose microcrystalline, croscarmellose sodium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate and polysorbate 80.

What Tandemact looks like and contents of the pack:

The tablets are white to off-white, round, convex and embossed ‘4833 G’ on one face and 30/2 on the other. The tablets are supplied in blister packs containing either 14, 28, 30, 50, 90 or 98 tablets.

Marketing Authorisation Holder and Manufacturer:

Marketing authorisation holder: Takeda Global Research and Development Centre (Europe) Ltd, 61 Aldwych, London, WC2B 4AE, United Kingdom.

Manufacturer: Takeda Ireland Limited, Bray Business Park, Kilruddery, County Wicklow, Ireland. Takeda Italia Farmaceutici S.p.A., Via Crosa, 86, 28065 Cerano (NO), Italy.

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This leaflet was last approved in {date}

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

PACKAGE LEAFLET: INFORMATION FOR THE USER
Tandemact 30 mg/4 mg tablets

Pioglitazone /glimepiride

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- If you are already taking other medicines for the treatment of diabetes.
- If you are under 18 years of age because use in such patients is not recommended.

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- flatulence
- localised swelling (oedema)
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- numbness

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- headache
- sinusitis
- vertigo
- abnormal vision
- sweating
- tiredness
- sleeplessness
- decreased blood sugar
- sugar in urine
- proteins in urine
- increased appetite

Rare: affects 1 to 10 users in 10,000
- noticeable changes in the blood
- risk of bone fracture
- risk of heart failure

Very rare: affects less than 1 user in 10,000
- liver disease
- allergic reactions including allergic shock
- nausea, vomiting and diarrhoea
- abdominal pain
- abdominal pressure
- feeling of fullness in the stomach
- decrease in the number of blood cells known as platelets

- sensitivity to light
- decrease in sodium concentrations in the blood

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This leaflet was last approved in {date}

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PACKAGE LEAFLET: INFORMATION FOR THE USER
Tandemact 45 mg/4 mg tablets

Pioglitazone /glimepiride

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Tandemact is used when metformin is not suitable for the treatment of type 2 (non-insulin dependent) diabetes mellitus. This is the diabetes that usually develops in adulthood.

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- cold or runny nose
- numbness

Uncommon: affects 1 to 10 users in 1000
- bladder cancer
- headache
- sinusitis
- vertigo
- abnormal vision
- sweating
- tiredness
- sleeplessness
- decreased blood sugar
- sugar in urine
- proteins in urine
- increased appetite

Rare: affects 1 to 10 users in 10,000
- noticeable changes in the blood
- risk of bone fracture
- risk of heart failure

Very rare: affects less than 1 user in 10,000
- liver disease
- allergic reactions including allergic shock
- nausea, vomiting and diarrhoea
- abdominal pain
- abdominal pressure
- feeling of fullness in the stomach

- decrease in the number of blood cells known as platelets
- sensitivity to light
- decrease in sodium concentrations in the blood

Blurred vision due to swelling (or fluid) in the back of the eye has been reported. If you experience these symptoms for the first time or if they get worse talk to your doctor as soon as possible. It is important to know what symptoms to expect when hypoglycaemia (low blood sugar) occurs. Ask your doctor or pharmacist for more information if you are not sure how to recognise this. The symptoms may include cold sweat, tiredness, headache, rapid heartbeat, hunger pangs, irritability, nervousness or nausea. Tell your doctor if you notice such symptoms.

Lowering of the Hb level and breakdown of red blood cells (haemolytic anemia) can occur in patients missing the enzyme Glucose-6-phosphodehydrogenase.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. STORING TANDEMACT

Keep out of the reach and sight of children.

Do not use Tandemact after the expiry date which is stated on the carton and blister.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via waste water or household waste. Ask you pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Tandemact contains:

The active substances are pioglitazone and glimepiride. Each tablet contains 45 mg pioglitazone (as hydrochloride) and 4 mg glimepiride. The other ingredients are cellulose microcrystalline, croscarmellose sodium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate and polysorbate 80.

What Tandemact looks like and contents of the pack:

The tablets are white to off-white, round, flat and embossed ‘4833 G’ on one face and ‘45/4’ on the other. The tablets are supplied in blister packs containing either 14, 28, 30, 50, 90, or 98 tablets.

Marketing Authorisation Holder and Manufacturer:

Marketing authorisation holder: Takeda Global Research and Development Centre (Europe) Ltd, 61 Aldwych, London, WC2B 4AE, United Kingdom.

Manufacturer: Takeda Ireland Limited, Bray Business Park, Kilruddery, County Wicklow, Ireland. Takeda Italia Farmaceutici S.p.A., Via Crosa, 86, 28065 Cerano (NO), Italy.

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in {date}

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/