ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tandemact 30 mg/2 mg tablets
Tandemact 30 mg/4 mg tablets
Tandemact 45 mg/4 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect
Each tablet contains approximately 125 mg lactose monohydrate (see section 4.4).

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

Excipient with known effect
Each tablet contains approximately 177 mg lactose monohydrate (see section 4.4).

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

Excipient with known effect
Each tablet contains approximately 214 mg lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

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

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

Tandemact 45 mg/4 mg tablets
White to off-white, round, flat and debossed '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 adult 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 HbA_{1c}). 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

Posology

The recommended dose of Tandemact is one tablet taken once daily.

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.

Special populations
Elderly
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).

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

Hepatic impairment
Tandemact should not be used in patients with hepatic impairment (see section 4.3 and 4.4).

Paediatric population
The safety and efficacy of Tandemact in children and adolescents under 18 years of age have not been established. No data are available.

Method of administration

The tablets are taken orally shortly before or with the first main meal. The tablets should be swallowed with a glass of water.

4.3 Contraindications

Tandemact is contraindicated in patients with:

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, 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 (creatinine clearance < 30 ml/min)
- Pregnancy
- Breast-feeding (see section 4.6)

4.4 Special warnings and precautions for use

There is no clinical trial experience of other oral anti-hyperglycaemic medicinal products 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 post-marketing cases of cardiac failure reported 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. Post marketing cases of peripheral oedema and cardiac failure have also been reported in patients with concomitant use of pioglitazone and nonsteroidal anti-inflammatory drugs, including selective COX-2 inhibitors. 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 12,506 patients, 0.15%) than in control groups (7 cases from 10,212 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. Epidemiological studies have also suggested a small increased risk of bladder cancer in diabetic patients treated with pioglitazone, although not all studies identified a statistically significant increased risk.

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 elevated liver enzymes and hepatocellular dysfunction during post-marketing experience with pioglitazone and glimepiride (see section 4.8). Although in very rare cases fatal outcome has been reported, causal relationship has not been established.
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, the medicinal product 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.

Polycystic ovarian syndrome

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).

Others

An increased incidence in bone fractures in women was seen in a pooled analysis of adverse reactions reports of bone fracture from randomised, controlled, double blind clinical trials (see section 4.8).

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.

Some epidemiological studies have suggested a similarly increased risk of fracture in both men and women.

The risk of fractures should be considered in the long term care of patients treated with pioglitazone (see section 4.8).

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 total 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

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).

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.

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 sulphonylureas 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, azapropazone and oxyfenbutazone
insulin and oral antidiabetic products
metformin
salicylates and p-amino-salicylic acid
anabolic steroids and male sex hormones
chloramphenicol
clarithromycin
coumarin anticoagulants
disopyramide
fenfluramine
fibrates
angiotensin-converting enzyme (ACE) inhibitors
fluoxetine
allopurinol
sympatholytics
cyclo-, tro- and iphosphamides
sulphinpyrazone
certain long-acting sulphonamides
tetracyclines
MAO-inhibitors
quinolone antibiotics
probenecid
miconazole
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 doses) 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 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Tandemact is not recommended in women of childbearing potential not using contraception. If a patient wishes to become pregnant, treatment with Tandemact should be discontinued.

Pregnancy

Risk related to pioglitazone
There are no adequate data from the use of pioglitazone in pregnant women. Studies of pioglitazone in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Risk related to glimepiride
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 is contraindicated during pregnancy (see section 4.3). If a pregnancy occurs, treatment with Tandemact should be discontinued.

Breast-feeding

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.

Tandemact is contra-indicated during breast-feeding (see section 4.3).

Fertility

In animal fertility studies with pioglitazone, there was no effect on copulation, impregnation or fertility index.

4.7 Effects on ability to drive and use machines

Tandemact has minor influence on the ability to drive and use machines. 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 using 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 use machines in these circumstances.

Patients who experience visual disturbance should be cautious when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

Clinical trials have been conducted with co-administered pioglitazone and glimepiride (see section 5.1). Hypoglycaemic reactions mostly occur immediately due to the sulphonylurea component of Tandemact. Symptoms can almost always be promptly controlled by immediate intake of carbohydrates (sugar). This is a serious reaction which may occur uncommonly (≥ 1/1,000 to < 1/100) (see section 4.4). Moderate to severe thrombocytopenia, leucopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anaemia and pancytopenia may occur rarely (≥ 1/10,000 to < 1/1,000) (see section 4.4). Other reactions such as bone fracture, weight increase and oedema may occur commonly (≥ 1/100 to < 1/10) (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions reported in double-blind studies and post marketing experience are listed below as MedDRA preferred term by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing incidence followed by decreasing seriousness.

Adverse reaction	**Frequency of adverse reactions**		
	Pioglitazone	**Glimepiride**	**Tandemact**
Infections and infestations			
upper respiratory tract infection	common		common
sinusitis	uncommon		uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
bladder cancer	uncommon		uncommon
Blood and lymphatic system disorders			
changes in haematology[1]		rare	rare
Immune system disorders			
allergic shock[2]		very rare	very rare
allergic vasculitis[2]		very rare	very rare
hypersensitivity and allergic reactions[3]	not known		not known
Metabolism and nutrition disorders			
hypoglycaemia			uncommon
appetite increased			uncommon
Nervous system disorders			
dizziness			common
hypo-aesthesia	common		common
headache			uncommon
insomnia	uncommon		uncommon
Eye disorders			
visual disturbance[4]	common		uncommon
macular oedema	not known		not known
Ear and labyrinth disorders			
vertigo			uncommon
Gastrointestinal disorders[5]			
flatulence			common
vomiting		very rare	very rare
diarrhoea		very rare	very rare
nausea		very rare	very rare
abdominal pain		very rare	very rare
abdominal pressure		very rare	very rare

Adverse reaction	Frequency of adverse reactions		
	Pioglitazone	**Glimepiride**	**Tandemact**
feeling of fullness in the stomach		very rare	very rare
Hepatobiliary disorders[6]			
hepatitis		very rare	very rare
impairment of liver function (with cholestasis and jaundice)		very rare	very rare
Skin and subcutaneous tissue disorders			
sweating			uncommon
hypersensitivity to light		very rare	very rare
urticaria[2]		not known	not known
itching[2]		not known	not known
rash[2]		not known	not known
Musculoskeletal and connective tissue disorders			
bone fracture[7]	common		common
Renal and urinary disorders			
glycosuria			uncommon
proteinuria			uncommon
General disorders and administration site conditions			
oedema[8]			common
fatigue			uncommon
Investigations			
weight increased[9]	common	common	common
increased lactic dehydrogenase			uncommon
decrease in sodium serum concentrations		very rare	very rare
alanine aminotransferase increase[10]	not known		not known

Description of selected adverse reactions

[1] Moderate to severe thrombocytopenia, leucopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anaemia and pancyto-penia may occur. These are in general reversible upon discontinuation of treatment.

[2] In very rare cases mild hypersensitivity 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.

[3] Postmarketing reports of hypersensitivity reactions in patients treated with pioglitazone have been reported. These reactions include anaphylaxis, angioedema, and urticaria.

[4] 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 medicinal products.

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

[6] 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.

[7] A pooled analysis was conducted of adverse event reports of bone fractures from randomised, comparator controlled, double blind clinical trials in over 8,100 patients in the pioglitazone-treated groups and 7,400 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%; 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. The observed excess risk of fractures for women on pioglitazone in this study is therefore 0.5 fractures per 100 patient years of use. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%). Post-marketing, bone fractures have been reported in both male and female patients (see section 4.4).

[8] 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.

[9] 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.

[10] 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.

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. In this study in patients receiving pioglitazone and insulin, a higher percentage of patients with heart failure was observed in patients aged ≥ 65 years compared with those less than 65 years (9.7% compared to 4.0%). In patients on insulin with no pioglitazone the incidence of heart failure was 8.2% in those ≥ 65 years compared to 4.0% in patients less than 65 years. Heart failure has been reported with marketing use of pioglitazone, and more frequently when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical studies, 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 overdose 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 overdose 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) overdose hospitalisation 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: Drugs used in diabetes, combinations of oral blood glucose lowering drugs; ATC code: A10BD06.

Tandemact combines two antihyperglycaemic active substances with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes mellitus: 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.

Pioglitazone

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 significantly different to glibenclamide.

In PROactive, a cardiovascular outcome study, 5,238 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 medicinal products (beta blockers, ACE inhibitors, angiotensin II antagonists, calcium channel blockers, nitrates, diuretics, acetylsalicylic acid, 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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Tandemact in all subsets of the paediatric population in type 2 diabetes mellitus. See section 4.2 for information on paediatric use.

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%).

Biotransformation
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.

Linearity/non-linearity
Single dose studies demonstrate linearity of pharmacokinetics in the therapeutic dose range.

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).

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.

Linearity/non-linearity
There is a linear relationship between dose and both C_{max} and AUC (area under the time/concentration curve).

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 tumourigenic 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 Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

8. MARKETING AUTHORISATION NUMBERS

EU/1/06/366/005
EU/1/06/366/006
EU/1/06/366/007
EU/1/06/366/008
EU/1/06/366/009
EU/1/06/366/010
EU/1/06/366/011
EU/1/06/366/012
EU/1/06/366/013
EU/1/06/366/014
EU/1/06/366/015
EU/1/06/366/016
EU/1/06/366/017

EU/1/06/366/018
EU/1/06/366/019
EU/1/06/366/020
EU/1/06/366/021
EU/1/06/366/022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 January 2007
Date of latest renewal: 09 September 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Takeda Ireland Limited
Bray Business Park
Kilruddery
County Wicklow
Ireland

Delpharm Novara S.r.l.
Via Crosa 86,
28065 Cerano (NO)
Italy

Takeda GmbH
Production Site Oranienburg
Lehnitzstrasse 70 – 98
16515 Oranienburg,
Germany

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

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

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 agreed 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 highlights 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
28 tablets
30 tablets
50 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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 Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

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

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tandemact 30 mg/2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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
28 tablets
30 tablets
50 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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 Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

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

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tandemact 30 mg/4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

Read the package leaflet before use.

Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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 Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

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

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tandemact 45 mg/4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

EXP

4. BATCH NUMBER

Lot

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

EXP

4. BATCH NUMBER

Lot

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

EXP

4. BATCH NUMBER

Lot

5. OTHER

FOR CALENDARISED PACKS:

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tandemact 30 mg/2 mg tablets
Tandemact 30 mg/4 mg tablets
Tandemact 45 mg/4 mg tablets
pioglitazone/glimepiride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tandemact is and what it is used for

Tandemact contains pioglitazone and glimepiride which are anti-diabetic medicines, used to control blood sugar level.

It is used in adults when metformin is not suitable to treat type 2 (non-insulin dependent) diabetes mellitus. This type 2 diabetes usually develops in adulthood where the body either does not produce enough insulin (a hormone that controls blood sugar levels), or cannot effectively use the insulin it produces.

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. What you need to know before you take Tandemact

Do not take Tandemact:
- if you are allergic to pioglitazone, glimepiride, other sulphonylureas or sulphonamides, or any of the other ingredients of this medicine (listed in section 6)
- if you have heart failure or have had heart failure in the past
- if you have liver disease
- if you have diabetic ketoacidosis (a complication of diabetes with rapid weight loss, nausea or vomiting)
- 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 in a diabetic coma
- if you are pregnant
- if you are breast-feeding

Warnings and precautions
Talk to your doctor or pharmacist before taking Tandemact (see also section 4)
- if you have a problem with your heart. Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin together 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).
- if you retain water (fluid retention) or have heart failure problems in particular if you are over 75 years old. If you take anti-inflammatory medicines which can also cause fluid retention and swelling, you must also tell your doctor.
- if you have a special type of diabetic eye disease called macular oedema (swelling of the back of the eye), talk to your doctor if you notice any change to your vision.
- if you have a problem with your liver. Before you start taking Tandemact you will have a blood sample taken to check your liver function. This check should be repeated at intervals. Inform your doctor as soon as possible if you develop symptoms suggesting a problem with your liver (like feeling sick without explanations, vomiting, stomach ache, tiredness, loss of appetite and/or dark urine) as your liver function should be checked.
- if you have cysts on your ovaries (polycystic ovary syndrome). There may be an increased possibility of becoming pregnant because you may ovulate again when you take Tandemact. If this applies to you, use appropriate contraception to avoid the possibility of an unplanned pregnancy.
- if you are already taking other medicines for the treatment of diabetes.
- if you have problems with your enzyme called Glucose-6-phosphodehydrogenase since it can decrease your red cells.

You may also experience a reduction in blood count (anaemia). Your doctor may take blood tests to monitor your blood cell levels and liver function.

Hypoglycaemia
When you take Tandemact, your blood sugar could fall below the normal level (hypoglycaemia). If you experience symptoms of hypoglycaemia such as cold sweat, tiredness, headache, rapid heartbeat, hunger pangs, irritability, nervousness or nausea, you should take some sugar to increase your blood sugar level again. Ask your doctor or pharmacist for more information if you are not sure how to recognise this. It is recommended that you carry some sugar lumps, sweets, biscuits or sugary fruit juice.

Broken bones
A higher number of bone fractures was seen in patients, particularly women taking pioglitazone. Your doctor will take this into account when treating your diabetes.

Children and adolescents
Use in children and adolescents under 18 years is not recommended.

Other medicines and Tandemact
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because some medicines can weaken or strengthen the effect of Tandemact on the level of sugar in your blood.

The following medicines can increase the blood sugar lowering effect of Tandemact. This can lead to a risk of hypoglycaemia (low blood sugar):
- gemfibrozil and fibrates (to lower high cholesterol level)
- insulin, metformin or other medicines to treat diabetes mellitus
- phenylbutazone, azapropazone, oxyphenbutazone, aspirin-like medicines (to treat pain and inflammation)
- long acting sulphonamides, tetracyclines, chloramphenicol, fluconazole, miconazole, quinolones, clarithromycin (to treat bacterial or fungal infections)

- anabolic steroids (supporting muscle build up) or male sex hormone replacement therapy
- fluoxetine, MAO-inhibitors (to treat depression)
- angiotensin-converting enzyme (ACE) inhibitors, sympatholytics, disopyramide, pentoxifylline, coumarin derivatives such as warfarin (to treat heart or blood problems)
- allopurinol, probenecid, sulfinpyrazone (to treat gout)
- cyclophosphamide, ifosfamide, trofosfamide (to treat cancer)
- fenfluramine (to reduce weight)
- tritoqualine (to treat allergies)

The following medicines may decrease the blood sugar lowering effect of Tandemact. This can lead to a risk of hyperglycaemia (high blood sugar level):
- oestrogens, progestogens (female sex hormones)
- thiazide diuretics and saluretics also called water tablets (to treat high blood pressure)
- levothyroxine (to stimulate the thyroid gland)
- glucocorticoids (to treat allergies and inflammation)
- chlorpromazine and other phenothiazine derivatives (to treat severe mental disorders)
- adrenaline and sympathicomimetics (to increase heart beat, to treat asthma or nasal congestion, coughs and colds or used in life-threatening emergencies)
- nicotinic acid (to treat high cholesterol level)
- long-term use of laxatives (to treat constipation)
- phenytoin (to treat fits)
- barbiturates (to treat nervousness and sleep problems)
- azetazolamide (to treat increased pressure in the eye also called glaucoma)
- diazoxide (to treat high blood pressure or low blood sugar)
- rifampicin (to treat infections, tuberculosis)
- glucagon (to treat severe low blood sugar levels)

The following medicines can increase or decrease the blood sugar lowering effect of Tandemact:
- H_2 antagonists (to treat stomach ulcers)
- beta-blockers, clonidine, guanethidine and reserpine (to treat high blood pressure or heart failure). These can also hide the signs of hypoglycaemia, so special care is needed when taking these medicines

Tandemact may either increase or weaken the effects of the following medicines:
- coumarin derivatives such as warfarin (to slow down or stop blood clotting)

Tell your doctor or pharmacist if you are taking any of these. Your blood sugar will be checked, and your dose of Tandemact may need to be changed.

Tandemact with alcohol
Avoid alcohol while taking Tandemact since alcohol may increase or decrease the blood sugar lowering action of Tandemact in an unpredictable way.

Pregnancy and breast-feeding
Do not use Tandemact if you are pregnant. You must tell your doctor if you are, you think you may be pregnant or are planning to have a baby. Your doctor will advise you to discontinue this medicine.
Do not use Tandemact if you are breastfeeding or are planning to breast-feed (see section “Do not take Tandemact”).

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 use machines.
Take care if you experience abnormal vision.

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

3. How to take Tandemact

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one tablet taken once daily shortly before or with the first main meal. Your doctor will tell you the dose to take or if necessary to change to a different dose. You should swallow the tablets with a glass of water.

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.

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. Your blood sugar could fall below the normal level. The symptoms may include cold sweat, tiredness, headache, rapid heartbeat, hunger pangs, irritability, nervousness, nausea, coma or convulsion. Your blood sugar level can be increased by taking sugar. It is recommended that you carry some sugar lumps, sweets, biscuits or sugary fruit juice.

If you forget to take Tandemact
Take Tandemact daily as prescribed. However if you miss a dose, skip the missed dose and just carry on with the next dose as normal. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Tandemact
Tandemact should be used every day to work properly. If you stop using Tandemact, your blood sugar may go up. Talk to your doctor before stopping this treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

In particular, patients have experienced the following serious side effects:

Bladder cancer has been experienced uncommonly (may affect up to 1 in 100 people) 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.

Hypoglycaemia (low blood sugar) has been reported uncommonly (may affect up to 1 in 100 people) in patients taking Tandemact. The symptoms may include cold sweat, tiredness, headache, rapid heartbeat, hunger pangs, irritability, nervousness or nausea. 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 and what you should do if you experience the symptoms.

Decrease in blood platelets (which increases risk of bleeding or bruising), red blood cells (which makes the skin pale and cause weakness or breathlessness) and white blood cells(which makes infections more likely) have been reported in patients taking Tandemact rarely (may affect up to 1 in 1,000 people). If you experience this side effect, talk to your doctor as soon as possible. These problems generally get better after you stop taking Tandemact.

Localised swelling (oedema) has also been experienced commonly (may affect up to 1 in 10 people) in patients taking Tandemact in combination with insulin. If you experience this side effect, talk to your doctor as soon as possible.

Broken bones have been reported commonly (may affect up to 1 in 10 people) in female patients taking Tandemact and have also been reported in male patients (frequency cannot be estimated from the available data) taking Tandemact. If you experience this side effect, talk to your doctor as soon as possible.

Blurred vision due to swelling (or fluid) at the back of the eye (macular oedema) has also been reported in patients taking Tandemact (frequency cannot be estimated from the available data). If you experience this symptom for the first time, talk to your doctor as soon as possible. Also, if you already have blurred vision and the symptom gets worse, talk to your doctor as soon as possible.

Allergic reactions have been reported with frequency not known (cannot be estimated from the available data) in patients taking Tandemact. If you have a serious allergic reaction, including hives and swelling of the face, lips, tongue, or throat that may cause difficulty in breathing or swallowing stop taking this medicine and talk to your doctor immediately.

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

Common (may affect up to 1 in 10 people)

- weight gain
- dizziness
- gas
- respiratory infection
- numbness

Uncommon (may affect up to 1 in 100 people)

- headache
- inflammation of the sinuses (sinusitis)
- vertigo
- abnormal vision
- sweating
- tiredness
- difficulty sleeping (insomnia)
- decreased blood sugar
- sugar in urine
- proteins in urine
- increased appetite
- increase of an enzyme called lactic dehydrogenase (LDH)

Rare (may affect up to 1 in 1,000 people)
- noticeable changes in blood

Very rare (may affect up to 1 in 10,000 people)
- liver disease

- allergic reactions including allergic shock
- feeling sick (nausea), vomiting and diarrhoea
- stomach ache
- abdominal pressure
- feeling of fullness in the stomach
- sensitivity to light
- decrease in salt (sodium) concentrations in the blood

Not known (frequency can not be estimated from the available data)
- increase in liver enzymes
- itchy skin
- raised and itchy rash (hives)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tandemact

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via waste water or household waste. Ask you pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tandemact contains
- The active substances are pioglitazone and glimepiride.
  Each Tandemact 30 mg/2 mg tablet contains 30 mg pioglitazone (as hydrochloride) and 2 mg glimepiride.
  Each Tandemact 30 mg/4 mg tablet contains 30 mg pioglitazone (as hydrochloride) and 4 mg glimepiride.
  Each Tandemact 45 mg/4 mg tablet contains 45 mg pioglitazone (as hydrochloride) and 4 mg glimepiride.
- The other ingredients are cellulose microcrystalline, croscarmellose sodium, hydroxypropylcellulose, lactose monohydrate (see section 2 'Tandemact contains lactose monohydrate'), magnesium stearate and polysorbate 80.

What Tandemact looks like and contents of the pack
- Tandemact 30 mg/2 mg tablets are white to off-white, round, convex and debossed '4833 G' on one face and '30/2' on the other.
- Tandemact 30 mg/4 mg tablets are white to off-white, round, convex and debossed '4833 G' on one face and '30/4' on the other.
- Tandemact 45 mg/4 mg tablets are white to off-white, round, flat and debossed '4833 G' on one face and '45/4' on the other.

The tablets are supplied in aluminium/aluminium blister packs containing either 14, 28, 30, 50, 90 or 98 tablets.

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu