ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paglitaz 15 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg of pioglitazone (as hydrochloride).

Excipient with known effect:
Each tablet contains 88.83 mg of lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White to almost white round tablets with bevelled edges and with engraved "15" on one side of tablet (diameter 7.0 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pioglitazone is indicated as second or third line in the treatment of type 2 diabetes mellitus as described below:

as **monotherapy**
- in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance;

as **dual oral therapy** in combination with
- metformin, in adult patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin;
- a sulphonylurea, only in adult patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulphonylurea;

as **triple oral therapy** in combination with
- metformin and a sulphonylurea, in adult patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

- Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus in adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance (see section 4.4).

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

Posology

Pioglitazone treatment may be initiated at 15 mg or 30 mg once daily. The dose may be increased in increments up to 45 mg once daily.
In combination with insulin, the current insulin dose can be continued upon initiation of pioglitazone therapy. If patients report hypoglycaemia, the dose of insulin should be decreased.

Special population

Older people

No dose 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

No dose adjustment is necessary in patients with impaired renal function (creatinine clearance > 4 ml/min) (see section 5.2). No information is available from dialysed patients therefore pioglitazone should not be used in such patients.

Patients with hepatic impairment

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

Paediatric population

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

Method of administration

Pioglitazone tablets are taken orally once daily with or without food. Tablets should be swallowed with a glass of water.

4.3 Contraindications

Pioglitazone is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- cardiac failure or history of cardiac failure (NYHA stages I to IV),
- hepatic impairment,
- diabetic ketoacidosis,
- current bladder cancer or a history of bladder cancer,
- uninvestigated macroscopic haematuria.

4.4 Special warnings and precautions for use

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 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. Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin. 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. Pioglitazone should be discontinued if any deterioration in cardiac status 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.

Older people

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.

Monitoring of liver function

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

Following initiation of therapy with pioglitazone it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3 times the upper limit of normal during pioglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 times 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 pioglitazone 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 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

There was a small reduction in mean haemoglobin (4% relative reduction) and haematocrit (4.1% relative reduction) during therapy with pioglitazone, 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.

Hypoglycaemia

As a consequence of increased insulin sensitivity, patients receiving pioglitazone in dual or triple oral therapy with a sulphonylurea or in dual therapy with insulin may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulphonylurea or insulin may be necessary.

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 reactions 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%).

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.

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).

Paglitaz 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

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. Since there is a potential for an increase in dose-related adverse events, 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate human data to determine the safety of pioglitazone during pregnancy. 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. The relevance of such a mechanism in humans is unclear and pioglitazone should not be used in pregnancy.

Breast-feeding

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, pioglitazone should not be administered to breast-feeding women.

Fertility

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

4.7 Effects on ability to drive and use machines

Pioglitazone has no or negligible influence on the ability to drive and use machines. However patients who experience visual disturbance should be cautious when driving or using machines.

4.8 Undesirable effects

Adverse reactions reported in excess (> 0.5%) of placebo and as more than an isolated case in patients receiving pioglitazone in double-blind studies 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 frequency grouping, adverse reactions are presented in order of decreasing incidence and seriousness.

Tabulated list of adverse reactions

Adverse reaction	**Frequency of adverse reactions of pioglitazone by treatment regimen**				
	Mono-therapy	**Combination**			
		with metformin	**with sulpho-nylurea**	**with metformin and sulpho-nylurea**	**with insulin**
Infections and infestations					
upper respiratory tract infection	common	common	common	common	common
bronchitis					common
sinusitis	uncommon	uncommon	uncommon	uncommon	uncommon
Blood and lymphatic system disorders					
anaemia		common			
Immune System Disorders					
Hypersensitivity and allergic reactions[1]	not known	not known	not known	not known	not known
Metabolism and nutrition disorders					
hypo-glycaemia			uncommon	very common	common
appetite increased			uncommon		
Nervous system disorders					
hypo-aesthesia	common	common	common	common	common
headache		common	uncommon		
dizziness			common		
insomnia	uncommon	uncommon	uncommon	uncommon	uncommon
Eye disorders					

Adverse reaction	Frequency of adverse reactions of pioglitazone by treatment regimen				
		Combination			
	Mono-therapy	with metformin	with sulpho-nylurea	with metformin and sulpho-nylurea	with insulin
visual disturbance[2]	common	common	uncommon		
macular oedema[3]	not known	not known	not known	not known	not known
Ear and labyrinth disorders					
vertigo			uncommon		
Cardiac disorders					
heart failure[4]					common
Neoplasms benign, malignant and unspecified (including cysts and polyps)					
bladder cancer	uncommon	uncommon	uncommon	uncommon	uncommon
Respiratory, thoracic and mediastinal disorders					
dyspnoea					common
Gastrointestinal disorders					
flatulence		uncommon	common		
Skin and subcutaneous tissue disorders					
sweating			uncommon		
Musculoskeletal and connective tissue disorders					
fracture bone[5]	common	common	common	common	common
arthralgia		common		common	common
back pain					common
Renal and urinary disorders					
haematuria		common			
glycosuria			uncommon		
proteinuria			uncommon		
Reproductive system and breast disorders					
erectile dysfunction		common			
General disorders and					

Adverse reaction	Frequency of adverse reactions of pioglitazone by treatment regimen				
		Combination			
	Mono-therapy	with metformin	with sulpho-nylurea	with metformin and sulpho-nylurea	with insulin
administration site conditions					
oedema					very common
fatigue			uncommon		
Investigations					
weight increased[6]	common	common	common	common	common
blood creatine phospho-kinase increased				common	
increased lactic dehydro-genase			uncommon		
Alanine aminotransferase increased [7]	not known	not known	not known	not known	not known

Description of selected adverse reactions

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

[2]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 treatments.

[3]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.

[4]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 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.

[5]A pooled analysis was conducted of adverse reactions 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%).

[6]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 metformin resulted in mean weight increase over one year of 1.5 kg and added to a sulphonylurea of 2.8 kg. In comparator groups addition of sulphonylurea to metformin resulted in a mean weight gain of 1.3 kg and addition of metformin to a sulphonylurea a mean weight loss of 1.0 kg.

[7]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.

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

Symptoms
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.
Hypoglycaemia may occur in combination with sulphonylureas or insulin.

Management
Symptomatic and general supportive measures should be taken in case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins; ATC code: A10BG03.

Mechanism of action
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.

Pharmacodynamic effects
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.

Clinical efficacy and safety
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 HbA1c $\geq$ 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 HbA1c < 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 HbA1c was similar between treatment groups after one year. The rate of deterioration of HbA1c 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 HbA1c 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 medicinal products (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 incidences of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with pioglitazone 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

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.

Older people

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

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.

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.

5.3 Preclinical safety data

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.

Environmental Risk Assessment (ERA) : no environmental impact is anticipated from the clinical use of pioglitazone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hydroxypropylcellulose (E463)
Croscarmellose sodium
Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister packs (OPA/Al/PVC-Al foil): 14, 28, 30, 56, 60, 90 and 98 tablets in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

14 tablets: EU/1/11/721/001
28 tablets: EU/1/11/721/002
30 tablets: EU/1/11/721/003
56 tablets: EU/1/11/721/004
60 tablets: EU/1/11/721/005
90 tablets: EU/1/11/721/006
98 tablets: EU/1/11/721/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2012
Date of latest renewal:

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

1. NAME OF THE MEDICINAL PRODUCT

Paglitaz 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect:
Each tablet contains 176.46 mg of lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White to almost white round tablets with bevelled edges (diameter 8.0 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pioglitazone is indicated as second or third line in the treatment of type 2 diabetes mellitus as described below:

as **monotherapy**
- in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance;

as **dual oral therapy** in combination with
- metformin, in adult patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin;
- a sulphonylurea, only in adult patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulphonylurea;

as **triple oral therapy** in combination with
- metformin and a sulphonylurea, in adult patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

- Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus in adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance (see section 4.4).

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

Posology

Pioglitazone treatment may be initiated at 15 mg or 30 mg once daily. The dose may be increased in increments up to 45 mg once daily.
In combination with insulin, the current insulin dose can be continued upon initiation of pioglitazone therapy. If patients report hypoglycaemia, the dose of insulin should be decreased.

Special population

Older people

No dose 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

No dose adjustment is necessary in patients with impaired renal function (creatinine clearance > 4 ml/min) (see section 5.2). No information is available from dialysed patients therefore pioglitazone should not be used in such patients.

Patients with hepatic impairment

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

Paediatric population

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

Method of administration

Pioglitazone tablets are taken orally once daily with or without food. Tablets should be swallowed with a glass of water.

4.3 Contraindications

Pioglitazone is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- cardiac failure or history of cardiac failure (NYHA stages I to IV),
- hepatic impairment,
- diabetic ketoacidosis,
- current bladder cancer or a history of bladder cancer,
- uninvestigated macroscopic haematuria.

4.4 Special warnings and precautions for use

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 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. Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin. 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. Pioglitazone should be discontinued if any deterioration in cardiac status 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.

Older people

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.

Monitoring of liver function

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

Following initiation of therapy with pioglitazone it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3 times the upper limit of normal during pioglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 times 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 pioglitazone 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 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

There was a small reduction in mean haemoglobin (4% relative reduction) and haematocrit (4.1% relative reduction) during therapy with pioglitazone, 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.

Hypoglycaemia

As a consequence of increased insulin sensitivity, patients receiving pioglitazone in dual or triple oral therapy with a sulphonylurea or in dual therapy with insulin may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulphonylurea or insulin may be necessary.

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 reactions 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%).

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.

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).

Paglitaz 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

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. Since there is a potential for an increase in dose-related adverse events, 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate human data to determine the safety of pioglitazone during pregnancy. 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. The relevance of such a mechanism in humans is unclear and pioglitazone should not be used in pregnancy.

Breast-feeding

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, pioglitazone should not be administered to breast-feeding women.

Fertility

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

4.7 Effects on ability to drive and use machines

Pioglitazone has no or negligible influence on the ability to drive and use machines. However patients who experience visual disturbance should be cautious when driving or using machines.

4.8 Undesirable effects

Adverse reactions reported in excess (> 0.5%) of placebo and as more than an isolated case in patients receiving pioglitazone in double-blind studies 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 frequency grouping, adverse reactions are presented in order of decreasing incidence and seriousness.

Tabulated list of adverse reactions

Adverse reaction	**Frequency of adverse reactions of pioglitazone by treatment regimen**				
	Mono-therapy	**Combination**			
		with metformin	**with sulpho-nylurea**	**with metformin and sulpho-nylurea**	**with insulin**
Infections and infestations					
upper respiratory tract infection	common	common	common	common	common
bronchitis					common
sinusitis	uncommon	uncommon	uncommon	uncommon	uncommon
Blood and lymphatic system disorders					
anaemia		common			
Immune System Disorders					
Hypersensitivity and allergic reactions[1]	not known	not known	not known	not known	not known
Metabolism and nutrition disorders					
hypo-glycaemia			uncommon	very common	common
appetite increased			uncommon		
Nervous system disorders					
hypo-aesthesia	common	common	common	common	common
headache		common	uncommon		
dizziness			common		
insomnia	uncommon	uncommon	uncommon	uncommon	uncommon
Eye disorders					

Adverse reaction	Frequency of adverse reactions of pioglitazone by treatment regimen				
		Combination			
	Mono-therapy	with metformin	with sulpho-nylurea	with metformin and sulpho-nylurea	with insulin
visual disturbance[2]	common	common	uncommon		
macular oedema[3]	not known	not known	not known	not known	not known
Ear and labyrinth disorders					
vertigo			uncommon		
Cardiac disorders					
heart failure[4]					common
Neoplasms benign, malignant and unspecified (including cysts and polyps)					
bladder cancer	uncommon	uncommon	uncommon	uncommon	uncommon
Respiratory, thoracic and mediastinal disorders					
dyspnoea					common
Gastrointestinal disorders					
flatulence		uncommon	common		
Skin and subcutaneous tissue disorders					
sweating			uncommon		
Musculoskeletal and connective tissue disorders					
fracture bone[5]	common	common	common	common	common
arthralgia		common		common	common
back pain					common
Renal and urinary disorders					
haematuria		common			
glycosuria			uncommon		
proteinuria			uncommon		
Reproductive system and breast disorders					
erectile dysfunction		common			
General disorders and					

Adverse reaction	Frequency of adverse reactions of pioglitazone by treatment regimen				
		Combination			
	Mono-therapy	with metformin	with sulpho-nylurea	with metformin and sulpho-nylurea	with insulin
administration site conditions					
oedema					very common
fatigue			uncommon		
Investigations					
weight increased[6]	common	common	common	common	common
blood creatine phospho-kinase increased				common	
increased lactic dehydro-genase			uncommon		
Alanine aminotransferase increased [7]	not known	not known	not known	not known	not known

Description of selected adverse reactions

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

[2]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 treatments.

[3]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.

[4]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 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.

[5]A pooled analysis was conducted of adverse reactions 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%).

[6]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 metformin resulted in mean weight increase over one year of 1.5 kg and added to a sulphonylurea of 2.8 kg. In comparator groups addition of sulphonylurea to metformin resulted in a mean weight gain of 1.3 kg and addition of metformin to a sulphonylurea a mean weight loss of 1.0 kg.

[7]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.

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

Symptoms
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.
Hypoglycaemia may occur in combination with sulphonylureas or insulin.

Management
Symptomatic and general supportive measures should be taken in case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins; ATC code: A10BG03.

Mechanism of action
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.

Pharmacodynamic effects
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.

Clinical efficacy and safety

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 HbA1c ≥ 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 HbA1c < 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 HbA1c was similar between treatment groups after one year. The rate of deterioration of HbA1c 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 HbA1c 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 medicinal products (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 incidences of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies

with pioglitazone 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

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.

Older people

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

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.

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.

5.3 Preclinical safety data

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.

Environmental Risk Assessment (ERA): no environmental impact is anticipated from the clinical use of pioglitazone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hydroxypropylcellulose (E463)
Croscarmellose sodium
Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister packs (OPA/Al/PVC-Al foil): 14, 28, 30, 56, 60, 90 and 98 tablets in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

14 tablets: EU/1/11/721/008
28 tablets: EU/1/11/721/009
30 tablets: EU/1/11/721/010
56 tablets: EU/1/11/721/011
60 tablets: EU/1/11/721/012
90 tablets: EU/1/11/721/013
98 tablets: EU/1/11/721/014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2012
Date of latest renewal:

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

1. NAME OF THE MEDICINAL PRODUCT

Paglitaz 45 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect:
Each tablet contains 264.68 mg of lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White to almost white round tablets with bevelled edges and with engraved "45" on one side of tablet (diameter 10.0 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pioglitazone is indicated as second or third line in the treatment of type 2 diabetes mellitus as described below:

as **monotherapy**
- in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance;

as **dual oral therapy** in combination with
- metformin, in adult patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin;
- a sulphonylurea, only in adult patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulphonylurea;

as **triple oral therapy** in combination with
- metformin and a sulphonylurea, in adult patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

- Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus in adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance (see section 4.4).

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

Posology

Pioglitazone treatment may be initiated at 15 mg or 30 mg once daily. The dose may be increased in increments up to 45 mg once daily.
In combination with insulin, the current insulin dose can be continued upon initiation of pioglitazone therapy. If patients report hypoglycaemia, the dose of insulin should be decreased.

Special population

Older people

No dose 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

No dose adjustment is necessary in patients with impaired renal function (creatinine clearance > 4 ml/min) (see section 5.2). No information is available from dialysed patients therefore pioglitazone should not be used in such patients.

Patients with hepatic impairment

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

Paediatric population

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

Method of administration

Pioglitazone tablets are taken orally once daily with or without food. Tablets should be swallowed with a glass of water.

4.3 Contraindications

Pioglitazone is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- cardiac failure or history of cardiac failure (NYHA stages I to IV),
- hepatic impairment,
- diabetic ketoacidosis,
- current bladder cancer or a history of bladder cancer,
- uninvestigated macroscopic haematuria.

4.4 Special warnings and precautions for use

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 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. Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin. 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. Pioglitazone should be discontinued if any deterioration in cardiac status 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.

Older people

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.

Monitoring of liver function

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

Following initiation of therapy with pioglitazone it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3 times the upper limit of normal during pioglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 times 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 pioglitazone 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 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

There was a small reduction in mean haemoglobin (4% relative reduction) and haematocrit (4.1% relative reduction) during therapy with pioglitazone, 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.

Hypoglycaemia

As a consequence of increased insulin sensitivity, patients receiving pioglitazone in dual or triple oral therapy with a sulphonylurea or in dual therapy with insulin may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulphonylurea or insulin may be necessary.

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 reactions 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%).

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.

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).

Paglitaz 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

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. Since there is a potential for an increase in dose-related adverse events, 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate human data to determine the safety of pioglitazone during pregnancy. 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. The relevance of such a mechanism in humans is unclear and pioglitazone should not be used in pregnancy.

Breast-feeding

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, pioglitazone should not be administered to breast-feeding women.

Fertility

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

4.7 Effects on ability to drive and use machines

Pioglitazone has no or negligible influence on the ability to drive and use machines. However patients who experience visual disturbance should be cautious when driving or using machines.

4.8 Undesirable effects

Adverse reactions reported in excess (> 0.5%) of placebo and as more than an isolated case in patients receiving pioglitazone in double-blind studies 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 frequency grouping, adverse reactions are presented in order of decreasing incidence and seriousness.

Tabulated list of adverse reactions

Adverse reaction	**Frequency of adverse reactions of pioglitazone by treatment regimen**				
		Combination			
	Mono-therapy	**with metformin**	**with sulpho-nylurea**	**with metformin and sulpho-nylurea**	**with insulin**
Infections and infestations					
upper respiratory tract infection	common	common	common	common	common
bronchitis					common
sinusitis	uncommon	uncommon	uncommon	uncommon	uncommon
Blood and lymphatic system disorders					
anaemia		common			
Immune System Disorders					
Hypersensitivity and allergic reactions[1]	not known	not known	not known	not known	not known
Metabolism and nutrition disorders					
hypo-glycaemia			uncommon	very common	common
appetite increased			uncommon		
Nervous system disorders					
hypo-aesthesia	common	common	common	common	common
headache		common	uncommon		
dizziness			common		
insomnia	uncommon	uncommon	uncommon	uncommon	uncommon
Eye disorders					
visual disturbance[2]	common	common	uncommon		

Adverse reaction	Frequency of adverse reactions of pioglitazone by treatment regimen				
		Combination			
	Mono-therapy	with metformin	with sulpho-nylurea	with metformin and sulpho-nylurea	with insulin
macular oedema[3]	not known	not known	not known	not known	not known
Ear and labyrinth disorders					
vertigo			uncommon		
Cardiac disorders					
heart failure[4]					common
Neoplasms benign, malignant and unspecified (including cysts and polyps)					
bladder cancer	uncommon	uncommon	uncommon	uncommon	uncommon
Respiratory, thoracic and mediastinal disorders					
dyspnoea					common
Gastrointestinal disorders					
flatulence		uncommon	common		
Skin and subcutaneous tissue disorders					
sweating			uncommon		
Musculoskeletal and connective tissue disorders					
fracture bone[5]	common	common	common	common	common
arthralgia		common		common	common
back pain					common
Renal and urinary disorders					
haematuria		common			
glycosuria			uncommon		
proteinuria			uncommon		
Reproductive system and breast disorders					
erectile dysfunction		common			
General disorders and administration site conditions					

Adverse reaction	Frequency of adverse reactions of pioglitazone by treatment regimen				
		Combination			
	Mono-therapy	with metformin	with sulpho-nylurea	with metformin and sulpho-nylurea	with insulin
oedema					very common
fatigue			uncommon		
Investigations					
weight increased[6]	common	common	common	common	common
blood creatine phospho-kinase increased				common	
increased lactic dehydro-genase			uncommon		
Alanine aminotransferase increased [7]	not known	not known	not known	not known	not known

Description of selected adverse reactions

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

[2]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 treatments.

[3]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.

[4]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 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.

[5]A pooled analysis was conducted of adverse reactions 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%).

[6]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 metformin resulted in mean weight increase over one year of 1.5 kg and added to a sulphonylurea of 2.8 kg. In comparator groups addition of sulphonylurea to metformin resulted in a mean weight gain of 1.3 kg and addition of metformin to a sulphonylurea a mean weight loss of 1.0 kg.

[7]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.

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

Symptoms
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.
Hypoglycaemia may occur in combination with sulphonylureas or insulin.

Management
Symptomatic and general supportive measures should be taken in case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins; ATC code: A10BG03.

Mechanism of action
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.

Pharmacodynamic effects
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.

Clinical efficacy and safety
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 HbA1c $\geq$ 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 HbA1c < 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 HbA1c was similar between treatment groups after one year. The rate of deterioration of HbA1c 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 HbA1c 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 medicinal products (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 incidences of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with pioglitazone 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

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.

Older people

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

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.

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.

5.3 Preclinical safety data

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.

Environmental Risk Assessment (ERA): no environmental impact is anticipated from the clinical use of pioglitazone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hydroxypropylcellulose (E463)
Croscarmellose sodium
Magnesium stearate (E572)

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

Blister packs (OPA/Al/PVC-Al foil): 14, 28, 30, 56, 60, 90 and 98 tablets in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

14 tablets: EU/1/11/721/015
28 tablets: EU/1/11/721/016
30 tablets: EU/1/11/721/017
56 tablets: EU/1/11/721/018
60 tablets: EU/1/11/721/019
90 tablets: EU/1/11/721/020
98 tablets: EU/1/11/721/021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2012
Date of latest renewal:

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

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

TAD Pharma GmbH
Heinz-Lohmann-Straße 5
27472 Cuxhaven
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**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **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 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 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 FOLDING BOX

1. NAME OF THE MEDICINAL PRODUCT

Paglitaz 15 mg tablets

Pioglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 15 mg of pioglitazone (as hydrochloride).

3. LIST OF EXCIPIENTS

Contains also lactose monohydrate.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet.

14 tablets
28 tablets
30 tablets
56 tablets
60 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

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

14 tablets: EU/1/11/721/001
28 tablets: EU/1/11/721/002
30 tablets: EU/1/11/721/003
56 tablets: EU/1/11/721/004
60 tablets: EU/1/11/721/005
90 tablets: EU/1/11/721/006
98 tablets: EU/1/11/721/007

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Paglitaz 15 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Paglitaz 15 mg tablets

Pioglitazone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOLDING BOX

1. NAME OF THE MEDICINAL PRODUCT

Paglitaz 30 mg tablets

Pioglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains also lactose monohydrate.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet.

14 tablets
28 tablets
30 tablets
56 tablets
60 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

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

14 tablets: EU/1/11/721/008
28 tablets: EU/1/11/721/009
30 tablets: EU/1/11/721/010
56 tablets: EU/1/11/721/011
60 tablets: EU/1/11/721/012
90 tablets: EU/1/11/721/013
98 tablets: EU/1/11/721/014

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Paglitaz 30 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Paglitaz 30 mg tablets

Pioglitazone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOLDING BOX

1. NAME OF THE MEDICINAL PRODUCT

Paglitaz 45 mg tablets

Pioglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains also lactose monohydrate.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet.

14 tablets
28 tablets
30 tablets
56 tablets
60 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

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

14 tablets: EU/1/11/721/015
28 tablets: EU/1/11/721/016
30 tablets: EU/1/11/721/017
56 tablets: EU/1/11/721/018
60 tablets: EU/1/11/721/019
90 tablets: EU/1/11/721/020
98 tablets: EU/1/11/721/021

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Paglitaz 45 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Paglitaz 45 mg tablets

Pioglitazone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Paglitaz 15 mg tablets
Pioglitazone

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 Paglitaz is and what it is used for

Paglitaz contains pioglitazone. It is an anti-diabetic medicine used to treat type 2 (non-insulin dependent) diabetes mellitus, when metformin is not suitable or has failed to work adequately. This is the diabetes that usually develops in adulthood.

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

Paglitaz may be used on its own in patients who are unable to take metformin, and where treatment with diet and exercise has failed to control blood sugar or may be added to other therapies (such as metformin, sulphonylurea or insulin) which have failed to provide sufficient control in blood sugar.

2. What you need to know before you take Paglitaz

Do not take Paglitaz:
- if you are hypersensitive (allergic) to pioglitazone 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 had diabetic ketoacidosis (a complication of diabetes causing rapid weight loss, nausea or vomiting).
- if you have or ever had bladder cancer.
- if you have blood in your urine that your doctor has not checked.

Warnings and precautions
Talk to your doctor before taking Paglitaz:
- 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).
- if you have cysts on your ovaries (polycystic ovary syndrome). There may be an increased possibility of your becoming pregnant because you may ovulate again when you take Paglitaz. If this applies to you, use appropriate contraception to avoid the possibility of an unplanned pregnancy.
- if you have a problem with your liver or heart. Before you start taking Paglitaz you will have a blood sample taken to check your liver function. This check may be repeated at intervals. Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with Paglitaz 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).

If you take Paglitaz with other medicines for diabetes, it is more likely that your blood sugar could fall below the normal level (hypoglycaemia).

You may also experience a reduction in blood count (anaemia).

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 under 18 years is not recommended.

Other medicines and Paglitaz
Tell your doctor or pharmacist if you are taking , have recently taken or might take any other medicines.

You can usually continue to take other medicines whilst you are being treated with Paglitaz. However, certain medicines are especially likely to affect the amount of sugar in your blood:
- gemfibrozil (used to lower cholesterol)
- rifampicin (used to treat tuberculosis and other infections)

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

Paglitaz with food and drink
You may take your tablets with or without food. You should swallow the tablets with a glass of water.

Pregnancy and breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.Your doctor will advise you to discontinue this medicine.

Driving and using machines
Pioglitazone will not affect your ability to drive or use machines but take care if you experience abnormal vision.

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

3. How to take Paglitaz

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

One tablet should be taken once daily. If necessary your doctor may tell you to take a different dose. If you have the impression that the effect of Paglitaz is too weak, talk to your doctor.

When Paglitaz is taken in combination with other medicines used to treat diabetes (such as insulin, chlorpropamide, glibenclamide, gliclazide, tolbutamide) your doctor will tell you whether you need to take a smaller dose of your medicines.

Your doctor will ask you to have blood tests periodically during treatment with Paglitaz. This is to check that your liver is working normally.

If you are following a diabetic diet, you should continue with this while you are taking Paglitaz. Your weight should be checked at regular intervals; if your weight increases, inform your doctor.

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

If you take more Paglitaz than you should
If you accidentally take too many Paglitaz 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 and 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 Paglitaz
Take Paglitaz tablets daily as prescribed. However if you miss a dose, 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 Paglitaz
Paglitaz tablets should be used every day to work properly. If you stop using Paglitaz tablets, 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:

Heart failure has been experienced commonly (may affect up to 1 in 10 people) in patients taking Paglitaz in combination with insulin. Symptoms are unusual shortness of breath or rapid increase in weight or localised swelling (oedema). If you experience any of these, especially if you are over the age of 65, seek medical advice straight away.

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

Localised swelling (oedema) has also been experienced very commonly in patients taking Paglitaz 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 women patients taking Paglitaz. 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 (frequency not known) has also been reported in patients taking Paglitaz. 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 (frequency not known) in patients taking Paglitaz. 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 as soon as possible.

The other side effects that have been experienced by some patients taking Paglitaz are:

common (may affect up to 1 in 10 people)
- respiratory infection
- abnormal vision
- weight gain
- numbness

uncommon (may affect up to 1 in 100 people)
- inflammation of the sinuses (sinusitis)
- difficulty sleeping (insomnia)

not known (frequency cannot be estimated from the available data)
- increase in liver enzymes
- allergic reactions

The other side effects that have been experienced by some patients when Paglitaz is taken with other antidiabetic medicines are:

very common (may affect more than 1 in 10 people)
- decreased blood sugar (hypoglycaemia)

common (may affect up to 1 in 10 people)
- headache
- dizziness
- joint pain
- impotence
- back pain
- shortness of breath
- small reduction in red blood cell count
- flatulence

uncommon (may affect up to 1 in 100 people)
- sugar in urine, proteins in urine
- increase in enzymes
- spinning sensation (vertigo)
- sweating
- tiredness
- increased appetite

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 Paglitaz

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 packaging 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 wastewater or household waste. Ask your 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 Paglitaz contains
- The active substance is pioglitazone. Each tablet contains 15 mg of pioglitazone (as hydrochloride).
- The other ingredients are lactose monohydrate, hydroxypropylcellulose (E463), croscarmellose sodium, magnesium stearate (E572).

What Paglitaz looks like and contents of the pack
White to almost white round tablets with bevelled edges and with engraved "15" on one side of tablet (diameter 7.0 mm).

The tablets are available in boxes of 14, 28, 30, 56, 60, 90 and 98 tablets in blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

Manufacturer
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
TAD Pharma GmbH, Heinz-Lohmann-Straße 5, 27472 Cuxhaven, Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
KRKA, d.d., Novo mesto
Tél/Tel: + 32 (0)3 321 63 52

България
Представителство на KRKA в България
Тел.: + 359 (02) 962 34 50

Česká republika
KRKA ČR, s.r.o.
Tel: + 420 (0) 221 115 150

Danmark
KRKA Sverige AB
Tlf: + 46 (0)8 643 67 66 (SE)

Deutschland
TAD Pharma GmbH
Tel: + 49 (0) 4721 606-0

Lietuva
UAB KRKA Lietuva
Tel: + 370 5 236 27 40

Luxembourg/Luxemburg
KRKA, d.d., Novo mesto
Tél/Tel: + 32 (0)3 321 63 52

Magyarország
KRKA Magyarország Kereskedelmi Kft.
Tel.: + 361 (0) 355 8490

Malta
KRKA Pharma Dublin, Ltd.
Tel: + 353 1 293 91 80

Nederland
Focus Care Pharmaceuticals B.V.
Tel: +31 (0)75 61 20 511

Eesti
KRKA, d.d., Novo mesto Eesti filiaal
Tel: + 372 (0) 6 671 658

Ελλάδα
QUALIA PHARMA S.A.
Τηλ: +30 (0)210 2832941

España
KRKA Farmacéutica, S.L.
Tel: + 34 911 61 03 81

France
KRKA France Eurl
Tél: + 33 (0)1 57 40 82 25

Hrvatska
Krka – farma d.o.o.
Tel: + 385 1 6312 100

Ireland
KRKA Pharma Dublin, Ltd.
Tel: + 353 1 293 91 80

Ísland
KRKA Sverige AB
Sími: + 46 (0)8 643 67 66 (SE)

Italia
KRKA Farmaceutici Milano S.r.l.
Tel: + 39 02 3300 8841

Κύπρος
Kipa Pharmacal Ltd.
Τηλ: + 357 24 651 882

Latvija
KRKA Latvija SIA
Tel: + 371 6 733 86 10

Norge
KRKA Sverige AB
Tlf: + 46 (0)8 643 67 66 (SE)

Österreich
KRKA Pharma GmbH, Wien
Tel: + 43 (0)1 66 24 300

Polska
KRKA-POLSKA Sp. z o.o.
Tel.: + 48 (0)22 573 7500

Portugal
KRKA Farmacêutica, Sociedade Unipessoal Lda.
Tel: + 351 (0)21 46 43 650

România
KRKA Romania S.R.L., Bucharest
Tel: + 4 021 310 66 05

Slovenija
KRKA, d.d., Novo mesto
Tel: + 386 (0) 1 47 51 100

Slovenská republika
KRKA Slovensko, s.r.o.,
Tel: + 421 (0) 2 571 04 501

Suomi/Finland
KRKA Sverige AB
Puh/Tel: + 46 (0)8 643 67 66 (SE)

Sverige
KRKA Sverige AB
Tel: + 46 (0)8 643 67 66 (SE)

United Kingdom
Consilient Health (UK) Ltd.
Tel: + 44 (0)2089562310

This leaflet was last revised in <MM/YYYY>

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

Package leaflet: Information for the user

Paglitaz 30 mg tablets
Pioglitazone

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 Paglitaz is and what it is used for

Paglitaz contains pioglitazone. It is an anti-diabetic medicine used to treat type 2 (non-insulin dependent) diabetes mellitus, when metformin is not suitable or has failed to work adequately. This is the diabetes that usually develops in adulthood.

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

Paglitaz may be used on its own in patients who are unable to take metformin, and where treatment with diet and exercise has failed to control blood sugar or may be added to other therapies (such as metformin, sulphonylurea or insulin) which have failed to provide sufficient control in blood sugar.

2. What you need to know before you take Paglitaz

Do not take Paglitaz:
- if you are hypersensitive (allergic) to pioglitazone 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 had diabetic ketoacidosis (a complication of diabetes causing rapid weight loss, nausea or vomiting).
- if you have or ever had bladder cancer.
- if you have blood in your urine that your doctor has not checked.

Warnings and precautions
Talk to your doctor before taking Paglitaz:
- 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).
- if you have cysts on your ovaries (polycystic ovary syndrome). There may be an increased possibility of your becoming pregnant because you may ovulate again when you take Paglitaz. If this applies to you, use appropriate contraception to avoid the possibility of an unplanned pregnancy.
- if you have a problem with your liver or heart. Before you start taking Paglitaz you will have a blood sample taken to check your liver function. This check may be repeated at intervals. Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with Paglitaz 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).

If you take Paglitaz with other medicines for diabetes, it is more likely that your blood sugar could fall below the normal level (hypoglycaemia).

You may also experience a reduction in blood count (anaemia).

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 under 18 years is not recommended.

Other medicines and Paglitaz
Tell your doctor or pharmacist if you are taking , have recently taken or might take any other medicines.

You can usually continue to take other medicines whilst you are being treated with Paglitaz. However, certain medicines are especially likely to affect the amount of sugar in your blood:
- gemfibrozil (used to lower cholesterol)
- rifampicin (used to treat tuberculosis and other infections)

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

Paglitaz with food and drink
You may take your tablets with or without food. You should swallow the tablets with a glass of water.

Pregnancy and breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.Your doctor will advise you to discontinue this medicine.

Driving and using machines
Pioglitazone will not affect your ability to drive or use machines but take care if you experience abnormal vision.

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

3. How to take Paglitaz

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

One tablet should be taken once daily. If necessary your doctor may tell you to take a different dose. If you have the impression that the effect of Paglitaz is too weak, talk to your doctor.

When Paglitaz is taken in combination with other medicines used to treat diabetes (such as insulin, chlorpropamide, glibenclamide, gliclazide, tolbutamide) your doctor will tell you whether you need to take a smaller dose of your medicines.

Your doctor will ask you to have blood tests periodically during treatment with Paglitaz. This is to check that your liver is working normally.

If you are following a diabetic diet, you should continue with this while you are taking Paglitaz. Your weight should be checked at regular intervals; if your weight increases, inform your doctor.

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

If you take more Paglitaz than you should
If you accidentally take too many Paglitaz 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 and 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 Paglitaz
Take Paglitaz tablets daily as prescribed. However if you miss a dose, 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 Paglitaz
Paglitaz tablets should be used every day to work properly. If you stop using Paglitaz tablets, 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:

Heart failure has been experienced commonly (may affect up to 1 in 10 people) in patients taking Paglitaz in combination with insulin. Symptoms are unusual shortness of breath or rapid increase in weight or localised swelling (oedema). If you experience any of these, especially if you are over the age of 65, seek medical advice straight away.

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

Localised swelling (oedema) has also been experienced very commonly in patients taking Paglitaz 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 women patients taking Paglitaz. 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 (frequency not known) has also been reported in patients taking Paglitaz. 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 (frequency not known) in patients taking Paglitaz. 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 as soon as possible.

The other side effects that have been experienced by some patients taking Paglitaz are:

common (may affect up to 1 in 10 people)
- respiratory infection
- abnormal vision
- weight gain
- numbness

uncommon (may affect up to 1 in 100 people)
- inflammation of the sinuses (sinusitis)
- difficulty sleeping (insomnia)

not known (frequency cannot be estimated from the available data)
- increase in liver enzymes
- allergic reactions

The other side effects that have been experienced by some patients when Paglitaz is taken with other antidiabetic medicines are:

very common (may affect more than 1 in 10 people)
- decreased blood sugar (hypoglycaemia)

common (may affect up to 1 in 10 people)
- headache
- dizziness
- joint pain
- impotence
- back pain
- shortness of breath
- small reduction in red blood cell count
- flatulence

uncommon (may affect up to 1 in 100 people)
- sugar in urine, proteins in urine
- increase in enzymes
- spinning sensation (vertigo)
- sweating
- tiredness
- increased appetite

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 Paglitaz

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 packaging 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 wastewater or household waste. Ask your 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 Paglitaz contains
- The active substance is pioglitazone. Each tablet contains 30 mg of pioglitazone (as hydrochloride).
- The other ingredients are lactose monohydrate, hydroxypropylcellulose (E463), croscarmellose sodium, magnesium stearate (E572).

What Paglitaz looks like and contents of the pack
White to almost white round tablets with bevelled edges (diameter 8.0 mm).

The tablets are available in boxes of 14, 28, 30, 56, 60, 90 and 98 tablets in blisters.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

Manufacturer
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
TAD Pharma GmbH, Heinz-Lohmann-Straße 5, 27472 Cuxhaven, Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
KRKA, d.d., Novo mesto
Tél/Tel: + 32 (0)3 321 63 52

България
Представителство на KRKA в България
Тел.: + 359 (02) 962 34 50

Česká republika
KRKA ČR, s.r.o.
Tel: + 420 (0) 221 115 150

Danmark
KRKA Sverige AB
Tlf: + 46 (0)8 643 67 66 (SE)

Deutschland
TAD Pharma GmbH
Tel: + 49 (0) 4721 606-0

Eesti

Lietuva
UAB KRKA Lietuva
Tel: + 370 5 236 27 40

Luxembourg/Luxemburg
KRKA, d.d., Novo mesto
Tél/Tel: + 32 (0)3 321 63 52

Magyarország
KRKA Magyarország Kereskedelmi Kft.
Tel.: + 361 (0) 355 8490

Malta
KRKA Pharma Dublin, Ltd.
Tel: + 353 1 293 91 80

Nederland
Focus Care Pharmaceuticals B.V.
Tel: +31 (0)75 61 20 511

Norge

KRKA, d.d., Novo mesto Eesti filiaal
Tel: + 372 (0) 6 671 658

Ελλάδα
QUALIA PHARMA S.A.
Τηλ: +30 (0)210 2832941

España
KRKA Farmacéutica, S.L.
Tel: + 34 911 61 03 81

France
KRKA France Eurl
Tél: + 33 (0)1 57 40 82 25

Hrvatska
Krka – farma d.o.o.
Tel: + 385 1 6312 100

Ireland
KRKA Pharma Dublin, Ltd.
Tel: + 353 1 293 91 80

Ísland
KRKA Sverige AB
Sími: + 46 (0)8 643 67 66 (SE)

Italia
KRKA Farmaceutici Milano S.r.l.
Tel: + 39 02 3300 8841

Κύπρος
Kipa Pharmacal Ltd.
Τηλ: + 357 24 651 882

Latvija
KRKA Latvija SIA
Tel: + 371 6 733 86 10

KRKA Sverige AB
Tlf: + 46 (0)8 643 67 66 (SE)

Österreich
KRKA Pharma GmbH, Wien
Tel: + 43 (0)1 66 24 300

Polska
KRKA-POLSKA Sp. z o.o.
Tel.: + 48 (0)22 573 7500

Portugal
KRKA Farmacêutica, Sociedade Unipessoal Lda.
Tel: + 351 (0)21 46 43 650

România
KRKA Romania S.R.L., Bucharest
Tel: + 4 021 310 66 05

Slovenija
KRKA, d.d., Novo mesto
Tel: + 386 (0) 1 47 51 100

Slovenská republika
KRKA Slovensko, s.r.o.,
Tel: + 421 (0) 2 571 04 501

Suomi/Finland
KRKA Sverige AB
Puh/Tel: + 46 (0)8 643 67 66 (SE)

Sverige
KRKA Sverige AB
Tel: + 46 (0)8 643 67 66 (SE)

United Kingdom
Consilient Health (UK) Ltd.
Tel: + 44 (0)2089562310

This leaflet was last revised in <MM/YYYY>

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

Package leaflet: Information for the user

Paglitaz 45 mg tablets
Pioglitazone

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 Paglitaz is and what it is used for

Paglitaz contains pioglitazone. It is an anti-diabetic medicine used to treat type 2 (non-insulin dependent) diabetes mellitus, when metformin is not suitable or has failed to work adequately. This is the diabetes that usually develops in adulthood.

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

Paglitaz may be used on its own in patients who are unable to take metformin, and where treatment with diet and exercise has failed to control blood sugar or may be added to other therapies (such as metformin, sulphonylurea or insulin) which have failed to provide sufficient control in blood sugar.

2. What you need to know before you take Paglitaz

Do not take Paglitaz:
- if you are hypersensitive (allergic) to pioglitazone 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 had diabetic ketoacidosis (a complication of diabetes causing rapid weight loss, nausea or vomiting).
- if you have or ever had bladder cancer.
- if you have blood in your urine that your doctor has not checked.

Warnings and precautions
Talk to your doctor before taking Paglitaz:
- 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).
- if you have cysts on your ovaries (polycystic ovary syndrome). There may be an increased possibility of your becoming pregnant because you may ovulate again when you take Paglitaz. If this applies to you, use appropriate contraception to avoid the possibility of an unplanned pregnancy.
- if you have a problem with your liver or heart. Before you start taking Paglitaz you will have a blood sample taken to check your liver function. This check may be repeated at intervals. Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with Paglitaz 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).

If you take Paglitaz with other medicines for diabetes, it is more likely that your blood sugar could fall below the normal level (hypoglycaemia).

You may also experience a reduction in blood count (anaemia).

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 under 18 years is not recommended.

Other medicines and Paglitaz
Tell your doctor or pharmacist if you are taking , have recently taken or might take any other medicines.

You can usually continue to take other medicines whilst you are being treated with Paglitaz. However, certain medicines are especially likely to affect the amount of sugar in your blood:
- gemfibrozil (used to lower cholesterol)
- rifampicin (used to treat tuberculosis and other infections)

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

Paglitaz with food and drink
You may take your tablets with or without food. You should swallow the tablets with a glass of water.

Pregnancy and breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.Your doctor will advise you to discontinue this medicine.

Driving and using machines
Pioglitazone will not affect your ability to drive or use machines but take care if you experience abnormal vision.

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

3. How to take Paglitaz

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

One tablet should be taken once daily. If necessary your doctor may tell you to take a different dose. If you have the impression that the effect of Paglitaz is too weak, talk to your doctor.

When Paglitaz is taken in combination with other medicines used to treat diabetes (such as insulin, chlorpropamide, glibenclamide, gliclazide, tolbutamide) your doctor will tell you whether you need to take a smaller dose of your medicines.

Your doctor will ask you to have blood tests periodically during treatment with Paglitaz. This is to check that your liver is working normally.

If you are following a diabetic diet, you should continue with this while you are taking Paglitaz. Your weight should be checked at regular intervals; if your weight increases, inform your doctor.

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

If you take more Paglitaz than you should
If you accidentally take too many Paglitaz 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 and 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 Paglitaz
Take Paglitaz tablets daily as prescribed. However if you miss a dose, 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 Paglitaz
Paglitaz tablets should be used every day to work properly. If you stop using Paglitaz tablets, 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:

Heart failure has been experienced commonly (may affect up to 1 in 10 people) in patients taking Paglitaz in combination with insulin. Symptoms are unusual shortness of breath or rapid increase in weight or localised swelling (oedema). If you experience any of these, especially if you are over the age of 65, seek medical advice straight away.

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

Localised swelling (oedema) has also been experienced very commonly in patients taking Paglitaz 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 women patients taking Paglitaz. 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 (frequency not known) has also been reported in patients taking Paglitaz. 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 (frequency not known) in patients taking Paglitaz. 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 as soon as possible.

The other side effects that have been experienced by some patients taking Paglitaz are:

common (may affect up to 1 in 10 people)
- respiratory infection
- abnormal vision
- weight gain
- numbness

uncommon (may affect up to 1 in 100 people)
- inflammation of the sinuses (sinusitis)
- difficulty sleeping (insomnia)

not known (frequency cannot be estimated from the available data)
- increase in liver enzymes
- allergic reactions

The other side effects that have been experienced by some patients when Paglitaz is taken with other antidiabetic medicines are:

very common (may affect more than 1 in 10 people)
- decreased blood sugar (hypoglycaemia)

common (may affect up to 1 in 10 people)
- headache
- dizziness
- joint pain
- impotence
- back pain
- shortness of breath
- small reduction in red blood cell count
- flatulence

uncommon (may affect up to 1 in 100 people)
- sugar in urine, proteins in urine
- increase in enzymes
- spinning sensation (vertigo)
- sweating
- tiredness
- increased appetite

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 Paglitaz

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 packaging 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 wastewater or household waste. Ask your 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 Paglitaz contains
- The active substance is pioglitazone. Each tablet contains 45 mg of pioglitazone (as hydrochloride).
- The other ingredients are lactose monohydrate, hydroxypropylcellulose (E463), croscarmellose sodium, magnesium stearate (E572).

What Paglitaz looks like and contents of the pack
White to almost white round tablets with bevelled edges and with engraved "45" on one side of tablet (diameter 10.0 mm).

The tablets are available in boxes of 14, 28, 30, 56, 60, 90 and 98 tablets in blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

Manufacturer
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
TAD Pharma GmbH, Heinz-Lohmann-Straße 5, 27472 Cuxhaven, Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
KRKA, d.d., Novo mesto
Tél/Tel: + 32 (0)3 321 63 52

България
Представителство на KRKA в България
Тел.: + 359 (02) 962 34 50

Česká republika
KRKA ČR, s.r.o.
Tel: + 420 (0) 221 115 150

Danmark
KRKA Sverige AB
Tlf: + 46 (0)8 643 67 66 (SE)

Deutschland
TAD Pharma GmbH
Tel: + 49 (0) 4721 606-0

Lietuva
UAB KRKA Lietuva
Tel: + 370 5 236 27 40

Luxembourg/Luxemburg
KRKA, d.d., Novo mesto
Tél/Tel: + 32 (0)3 321 63 52

Magyarország
KRKA Magyarország Kereskedelmi Kft.
Tel.: + 361 (0) 355 8490

Malta
KRKA Pharma Dublin, Ltd.
Tel: + 353 1 293 91 80

Nederland
Focus Care Pharmaceuticals B.V.
Tel: +31 (0)75 61 20 511

Eesti
KRKA, d.d., Novo mesto Eesti filiaal
Tel: + 372 (0) 6 671 658

Ελλάδα
QUALIA PHARMA S.A.
Τηλ: +30 (0)210 2832941

España
KRKA Farmacéutica, S.L.
Tel: + 34 911 61 03 81

France
KRKA France Eurl
Tél: + 33 (0)1 57 40 82 25

Hrvatska
Krka – farma d.o.o.
Tel: + 385 1 6312 100

Ireland
KRKA Pharma Dublin, Ltd.
Tel: + 353 1 293 91 80

Ísland
KRKA Sverige AB
Sími: + 46 (0)8 643 67 66 (SE)

Italia
KRKA Farmaceutici Milano S.r.l.
Tel: + 39 02 3300 8841

Κύπρος
Kipa Pharmacal Ltd.
Τηλ: + 357 24 651 882

Latvija
KRKA Latvija SIA
Tel: + 371 6 733 86 10

Norge
KRKA Sverige AB
Tlf: + 46 (0)8 643 67 66 (SE)

Österreich
KRKA Pharma GmbH, Wien
Tel: + 43 (0)1 66 24 300

Polska
KRKA-POLSKA Sp. z o.o.
Tel.: + 48 (0)22 573 7500

Portugal
KRKA Farmacêutica, Sociedade Unipessoal Lda.
Tel: + 351 (0)21 46 43 650

România
KRKA Romania S.R.L., Bucharest
Tel: + 4 021 310 66 05

Slovenija
KRKA, d.d., Novo mesto
Tel: + 386 (0) 1 47 51 100

Slovenská republika
KRKA Slovensko, s.r.o.,
Tel: + 421 (0) 2 571 04 501

Suomi/Finland
KRKA Sverige AB
Puh/Tel: + 46 (0)8 643 67 66 (SE)

Sverige
KRKA Sverige AB
Tel: + 46 (0)8 643 67 66 (SE)

United Kingdom
Consilient Health (UK) Ltd.
Tel: + 44 (0)2089562310

This leaflet was last revised in <MM/YYYY>

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