Public Assessment Report

Decentralised Procedure

PIOGLITAZONE 15 MG, 30 MG AND 45 MG TABLETS

PIOGLITAZONE HYDROCHLORIDE

UK/H/3548/001-3/DC

UK Licence No: PL 14894/0655-7

RANBAXY (UK) LIMITED
On 22\textsuperscript{nd} March 2012, the UK granted Ranbaxy (UK) Limited Marketing Authorisations (licences) for Pioglitazone 15 mg, 30 mg and 45 mg Tablets.

Pioglitazone 15 mg, 30 mg and 45 mg Tablets contain the active ingredient, pioglitazone hydrochloride, which is an anti-diabetic medicine.

Pioglitazone 15 mg, 30 mg and 45 mg Tablets are used to treat type 2 (non-insulin dependent) diabetes mellitus.

Pioglitazone 15 mg, 30 mg and 45 mg Tablets are used in different ways; It can be used together with metformin or other agents such as sulphonylurea or insulin when they have not been effective in achieving control for diabetes.

It can be used alone to control diabetes when metformin is not tolerated or is has failed to work adequately and where diet plus exercise have failed to control the blood sugar.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Pioglitazone 15 mg, 30 mg and 45 mg Tablets outweigh the risks; hence these Marketing Authorisations have been granted.
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1 Introduction
2 Quality aspects
3 Non-clinical aspects
4 Clinical aspects
5 Overall conclusions

Module 6: Steps taken after initial procedure Not applicable
### Module 1

| **Product Name** | Pioglitazone 15 mg Tablets  
|                  | Pioglitazone 30 mg Tablets  
|                  | Pioglitazone 45 mg Tablets |
| **Type of Application** | Generic application, Article 10(1) |
| **Active Substance** | Pioglitazone hydrochloride |
| **Form** | Tablet |
| **Strength** | 15 mg  
|             | 30 mg  
|             | 45 mg  |
| **MA Holder** | Ranbaxy (UK) Limited  
|              | Building 4,  
|              | Chiswick Park,  
|              | 566 Chicwick High Road,  
|              | London  
|              | United Kingdom. |
| **Reference Member State (RMS)** | United Kingdom (UK) |
| **Concerned Member States (CMS)** | UK/H/3548/001/DC: France (FR), Portugal (PT) and Romania (RO)  
|                                  | UK/H/3548/002/DC: France (FR), the Netherlands (NL), Portugal (PT) and Romania (RO)  
|                                  | UK/H/3548/003/DC: Portugal (PT) and Romania (RO) |
| **Procedure Number** | UK/H/3548/001/DC  
|                      | UK/H/3548/002/DC  
|                      | UK/H/3548/003/DC |
| **End of Procedure** | Day 209: 22nd February 2012 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Pioglitazone 15 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Pioglitazone 15mg: Each tablet contains 16.53 mg Pioglitazone Hydrochloride, equivalent to 15 mg Pioglitazone
Excipients: Each tablet contains 34.77 mg lactose monohydrate.
For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Tablet
Pioglitazone 15mg:
The tablets are white to off white, round of about 5.0 mm diameter, flat beveled edge tablet, debossed with 'RB' on one side and '94' on the other side

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Pioglitazone is indicated as second or third line 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 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 15mg or 30mg once daily. The dose may be increased in increments up to 45mg 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
Elderly:
No dosage adjustment is necessary for elderly patients (see section 5.2). Physicians should start treatment with the lowest available dose and increase the dose gradually, particularly when pioglitazone is used in combination with insulin (see section 4.4 Fluid retention and cardiac failure).
Renal impairment:
No dosage 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.

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

Paediatric population
The safety and efficacy of Actos 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
- 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. 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.

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

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

Bladder Cancer
Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12506 patients, 0.15%) than in control groups (7 cases from 10212 patients, 0.07%) HR=2.64 (95% CI 1.11-6.31, P=0.029). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Available epidemiological data also suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone in particular in patients treated for the longest durations and with the highest cumulative doses. A possible risk after short term treatment cannot be excluded.
Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic haematuria should be investigated before starting pioglitazone therapy.

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

**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 X 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 X upper limit of normal during pioglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain> 3 X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with pioglitazone should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy 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 bone fracture from randomised, controlled, double blind clinical trials in over 8100 pioglitazone and 7400 comparator treated patients, on treatment for up to 3.5 years.

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

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

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

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

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

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

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

Pioglitazone 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 doserelated 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. Fetal 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 fetal growth. The relevance of such a mechanism in humans is unclear and pioglitazone should not be used in pregnancy.

Breastfeeding:
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 breastfeeding 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 effect 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 (> 1/1000 to < 1/100; rare (> 1/10000 to < 1/1000; very rare (< 1/10000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing incidences and seriousness.

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Frequency of adverse reactions of pioglitazone by treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monotherapy</td>
</tr>
<tr>
<td></td>
<td>with metformin</td>
</tr>
<tr>
<td></td>
<td>with metformin and sulphonylurea</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
</tr>
<tr>
<td>upper respiratory tract infection</td>
<td>common</td>
</tr>
<tr>
<td></td>
<td>common</td>
</tr>
<tr>
<td></td>
<td>common</td>
</tr>
<tr>
<td>bronchitis</td>
<td>uncommon</td>
</tr>
<tr>
<td>sinusitis</td>
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</tr>
<tr>
<td></td>
<td>uncommon</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>anaemia</td>
<td>common</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>hypo-glycaemia</td>
<td>uncommon</td>
</tr>
<tr>
<td></td>
<td>common</td>
</tr>
<tr>
<td>appetite increased</td>
<td>uncommon</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>hypo-aesthesia</td>
<td>common</td>
</tr>
<tr>
<td>headache</td>
<td>common</td>
</tr>
<tr>
<td>dizziness</td>
<td>common</td>
</tr>
<tr>
<td>insomnia</td>
<td>uncommon</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>visual disturbance1</td>
<td>common</td>
</tr>
<tr>
<td>macular oedema2</td>
<td>not known</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>not known</td>
</tr>
<tr>
<td></td>
<td>not known</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
</tr>
<tr>
<td>vertigo</td>
<td>uncommon</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
</tr>
<tr>
<td>heart failure3</td>
<td></td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>bladder cancer</td>
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**Respiratory, thoracic and mediastinal disorders**

<table>
<thead>
<tr>
<th>dyspnoea</th>
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<tbody>
<tr>
<td>common</td>
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**Gastrointestinal disorders**

<table>
<thead>
<tr>
<th>flatulence</th>
<th>uncommon</th>
<th>common</th>
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</thead>
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**Skin and subcutaneous tissue disorders**

<table>
<thead>
<tr>
<th>sweating</th>
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**Musculoskeletal and connective tissue disorders**

<table>
<thead>
<tr>
<th>fracture bone</th>
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<tbody>
<tr>
<td>arthralgia</td>
<td>common</td>
<td>common</td>
<td>common</td>
<td></td>
<td></td>
</tr>
<tr>
<td>back pain</td>
<td>common</td>
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**Renal and urinary disorders**

<table>
<thead>
<tr>
<th>haematuria</th>
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<tbody>
<tr>
<td>glycosuria</td>
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</tr>
<tr>
<td>proteinuria</td>
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**Reproductive system and breast disorders**

<table>
<thead>
<tr>
<th>erectile dysfunction</th>
<th>common</th>
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</table>

**General disorders and administration site conditions**

<table>
<thead>
<tr>
<th>oedema</th>
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<tbody>
<tr>
<td>very common</td>
<td></td>
</tr>
<tr>
<td>fatigue</td>
<td>uncommon</td>
</tr>
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**Investigations**

<table>
<thead>
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<th>weight increased</th>
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<th>common</th>
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<tbody>
<tr>
<td>blood creatine phospho-kinase increased</td>
<td>common</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>increased lactic dehydro-genase</td>
<td>uncommon</td>
<td></td>
<td></td>
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<tr>
<td>Alanine aminotransferase increased</td>
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<td>not known</td>
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</tr>
</tbody>
</table>

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1 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.

2 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.
3 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. Heart failure has been reported rarely with marketing use of pioglitazone, but more frequently when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure.

4 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%).

5 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.

6 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.

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

Hypoglycaemia may occur in combination with sulphonylureas or insulin. 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.

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

Fasting and postprandial glycaemic control is improved in patients with type 2 diabetes mellitus. The improved glycaemic control is associated with a reduction in both fasting and postprandial plasma insulin concentrations. A clinical trial of pioglitazone vs. gliclazide as monotherapy was extended to two years in order to assess time to treatment failure (defined as appearance of 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 medications (beta blockers, ACE inhibitors, angiotensin II antagonists, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates).

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

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.

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

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

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

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. Fetal 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 fetal 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: no environmental impact is anticipated from the clinical use of Pioglitazone.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose Monohydrate
Hydroxypropyl Cellulose
Carmellose Calcium
Magnesium Stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
1. Cold form blister pack comprises of oriented polyamide+ aluminium foil+ PVC film with the backing of hard tempered, aluminium foil coated with heat sealed lacquer on inner side.

Pack sizes (for all strengths): 14, 28, 30, 50, 56, 84, 90 and 98 tablets

2. Desiccant embedded cold form blister pack comprises of oriented polyamide, aluminium foil, PE + desiccant, HDPE coating with the lidding foil laminate (aluminium foil, heat seal extrusion coating)

Pack sizes (for all strengths): 14, 28, 30, 50, 56, 84, 90 and 98 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORITY
RANBAXY (UK) LIMITED
BUILDING 4, CHISWICK PARK
566 CHISWICK HIGH ROAD
LONDON
W4 5YE

8 MARKETING AUTHORIZATION NUMBER(S)
PL 14894/0655

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
22/03/2012

10 DATE OF REVISION OF THE TEXT
22/03/2012
1 NAME OF THE MEDICINAL PRODUCT
Pioglitazone 30 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Pioglitazone 30mg: Each tablet contains 33.06 mg Pioglitazone Hydrochloride, equivalent to 30 mg Pioglitazone.
Excipients: Each tablet contains 69.54 mg lactose monohydrate.

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Tablet

Pioglitazone 30mg:
The tablets are white to off white, round of about 7.0 mm diameter, flat beveled edge tablet debossed with 'RB' on one side and '95' on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Pioglitazone is indicated as second or third line 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 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 15mg or 30mg once daily. The dose may be increased in increments up to 45mg 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
Elderly:
No dosage adjustment is necessary for elderly patients (see section 5.2). Physicians should start treatment with the lowest available dose and increase the dose gradually, particularly when pioglitazone is used in combination with insulin (see section 4.4 Fluid retention and cardiac failure).
Renal impairment:
No dosage 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.

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

Paediatric population
The safety and efficacy of Actos 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
- 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. 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.

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

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

Bladder Cancer
Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12506 patients, 0.15%) than in control groups (7 cases from 10212 patients, 0.07%) HR=2.64 (95% CI 1.11-6.31, P=0.029). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Available epidemiological data also suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone in particular in patients treated for the longest durations and with the highest cumulative doses. A possible risk after short term treatment cannot be excluded.
Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic haematuria should be investigated before starting pioglitazone therapy.

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

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 X 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 X upper limit of normal during pioglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with pioglitazone should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy 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 bone fracture from randomised, controlled, double blind clinical trials in over 8100 pioglitazone and 7400 comparator treated patients, on treatment for up to 3.5 years.

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

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

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

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

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

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

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

Pioglitazone 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 doserelated 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. Fetal 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 fetal growth. The relevance of such a mechanism in humans is unclear and pioglitazone should not be used in pregnancy.

**Breastfeeding:**

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 breastfeeding 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 effect 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 (> 1/1000 to < 1/100; rare (> 1/10,000 to < 1/1,000; very rare (< 1/10000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing incidences and seriousness.

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Frequency of adverse reactions of pioglitazone by treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monotherapy</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>upper respiratory tract infection</td>
<td>common</td>
</tr>
<tr>
<td>bronchitis</td>
<td></td>
</tr>
<tr>
<td>sinusitis</td>
<td>uncommon</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>anaemia</td>
<td>common</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>hypo-glycaemia</td>
<td></td>
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<tr>
<td>appetite increased</td>
<td></td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>hypo-aesthesia</td>
<td>common</td>
</tr>
<tr>
<td>headache</td>
<td></td>
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<tr>
<td>dizziness</td>
<td></td>
</tr>
<tr>
<td>insomnia</td>
<td>uncommon</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>visual disturbance1</td>
<td>common</td>
</tr>
<tr>
<td>macular oedema2</td>
<td>not known</td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
</tr>
<tr>
<td>vertigo</td>
<td></td>
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<tr>
<td>Cardiac disorders</td>
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<tr>
<td>heart failure3</td>
<td></td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
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<tr>
<td>---</td>
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<tr>
<td>bladder cancer</td>
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<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
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<tr>
<td>dyspnoea</td>
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<table>
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<th>Gastrointestinal disorders</th>
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<th>Skin and subcutaneous tissue disorders</th>
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<tbody>
<tr>
<td>sweating</td>
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<table>
<thead>
<tr>
<th>Musculoskeletal and connective tissue disorders</th>
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<tbody>
<tr>
<td>fracture bone4</td>
<td>common</td>
</tr>
<tr>
<td>arthralgia</td>
<td>common</td>
</tr>
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<td>back pain</td>
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<table>
<thead>
<tr>
<th>Renal and urinary disorders</th>
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<tbody>
<tr>
<td>haematuria</td>
<td>common</td>
</tr>
<tr>
<td>glycosuria</td>
<td>uncommon</td>
</tr>
<tr>
<td>proteinuria</td>
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<thead>
<tr>
<th>Reproductive system and breast disorders</th>
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<tbody>
<tr>
<td>erectile dysfunction</td>
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<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
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</thead>
<tbody>
<tr>
<td>oedema</td>
<td></td>
</tr>
<tr>
<td>fatigue</td>
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<table>
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<tr>
<th>Investigations</th>
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<tr>
<td>weight increased5</td>
<td>common</td>
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<tr>
<td>blood creatine phospho-kinase increased</td>
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<tr>
<td>increased lactic dehydro-genase</td>
<td>uncommon</td>
</tr>
<tr>
<td>Alanine aminotransferase increased 6</td>
<td>not known</td>
</tr>
</tbody>
</table>

1 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.

2 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.
3 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. Heart failure has been reported rarely with marketing use of pioglitazone, but more frequently when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure.

4 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%).

5 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.

6 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.

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

Hypoglycaemia may occur in combination with sulphonylureas or insulin. 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.

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

Fasting and postprandial glycaemic control is improved in patients with type 2 diabetes mellitus. The improved glycaemic control is associated with a reduction in both fasting and postprandial plasma insulin concentrations. A clinical trial of pioglitazone vs. gliclazide as monotherapy was extended to two years in order to assess time to treatment failure (defined as appearance of 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 in clinical trials of up to two years duration, pioglitazone reduced total plasma triglycerides and free fatty acids, and increased HDL cholesterol levels, compared with placebo, metformin or gliclazide.

Pioglitazone did not cause statistically significant increases in LDL cholesterol levels compared with placebo, whilst reductions were observed with metformin and gliclazide. In a 20-week study, as well as reducing fasting triglycerides, pioglitazone reduced post prandial hypertriglyceridaemia through an effect on both absorbed and hepatically synthesised triglycerides. These effects were independent of pioglitazone's effects on glycaemia and were statistically significant different to glibenclamide.

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

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

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.

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

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

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

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. Fetal 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 fetal 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: no environmental impact is anticipated from the clinical use of Pioglitazone.
6  PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose Monohydrate
Hydroxypropyl Cellulose
Carmellose Calcium
Magnesium Stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
1. Cold form blister pack comprises of oriented polyamide+ aluminium foil+ PVC film with the backing of hard tempered, aluminium foil coated with heat sealed lacquer on inner side.

Pack sizes (for all strengths): 14, 28, 30, 50, 56, 84, 90 and 98 tablets

2. Desiccant embedded cold form blister pack comprises of oriented polyamide, aluminium foil, PE + desiccant, HDPE coating with the lidding foil laminate (aluminium foil, heat seal extrusion coating)

Pack sizes (for all strengths): 14, 28, 30, 50, 56, 84, 90 and 98 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal
No special requirements

7  MARKETING AUTHORISATION HOLDER
RANBAXY (UK) LIMITED
BUILDING 4, CHISWICK PARK
566 CHISWICK HIGH ROAD
LONDON
W4 5YE

8  MARKETING AUTHORISATION NUMBER(S)
PL 14894/0656

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/03/2012

10 DATE OF REVISION OF THE TEXT
22/03/2012
1 NAME OF THE MEDICINAL PRODUCT
Pioglitazone 45 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Pioglitazone 45mg: Each tablet contains 49.59 mg Pioglitazone Hydrochloride, equivalent to 45 mg Pioglitazone.
Excipients: Each tablet contains 104.31 mg lactose monohydrate.
For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Tablet
Pioglitazone 45mg:
The tablets are white to off white, round of about 8.0 mm diameter, flat beveled edge tablet, debossed with 'RB' on one side and '96' on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Pioglitazone is indicated as second or third line 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 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 15mg or 30mg once daily. The dose may be increased in increments up to 45mg 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
Elderly:
No dosage adjustment is necessary for elderly patients (see section 5.2). Physicians should start treatment with the lowest available dose and increase the dose gradually, particularly when pioglitazone is used in combination with insulin (see section 4.4 Fluid retention and cardiac failure).

Renal impairment:
No dosage 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.
Hepatic impairment:
Pioglitazone should not be used in patients with hepatic impairment (see sections 4.3 and 4.4).

Paediatric population
The safety and efficacy of Actos 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
- 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. 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.

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

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

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

Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic haematuria should be investigated before starting pioglitazone therapy.
Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

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 X 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 X upper limit of normal during pioglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain> 3 X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with pioglitazone should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy 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 bone fracture from randomised, controlled, double blind clinical trials in over 8100 pioglitazone and 7400 comparator treated patients, on treatment for up to 3.5 years.

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

The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this dataset on pioglitazone is therefore 0.8 fractures per 100 patient years of use.
In the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%; 1.0 fractures per 100 patient years) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures per 100 patient years) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).

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

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

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

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

Pioglitazone 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. Fetal 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 fetal growth. The relevance of such a mechanism in humans is unclear and pioglitazone should not be used in pregnancy.

**Breastfeeding:**

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 breastfeeding 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 effect 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 (> 1/1000 to < 1/100; rare (> 1/10000 to < 1/1000; very rare (< 1/10000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing incidences and seriousness.

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Frequency of adverse reactions of pioglitazone by treatment regimen</th>
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<tbody>
<tr>
<td></td>
<td>Monotherapy</td>
</tr>
<tr>
<td></td>
<td>with metformin</td>
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<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
</tr>
<tr>
<td>upper respiratory tract infection</td>
<td>common</td>
</tr>
<tr>
<td>bronchitis</td>
<td>common</td>
</tr>
<tr>
<td>sinusitis</td>
<td>uncommon</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>anaemia</td>
<td>common</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
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<tr>
<td>hypo-glycaemia</td>
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<tr>
<td>appetite increased</td>
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<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>hypo-aesthesia</td>
<td>common</td>
</tr>
<tr>
<td>headache</td>
<td>common</td>
</tr>
<tr>
<td>dizziness</td>
<td>common</td>
</tr>
<tr>
<td>insomnia</td>
<td>uncommon</td>
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<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>visual disturbance</td>
<td>common</td>
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<tr>
<td>macular oedema</td>
<td>not known</td>
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<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
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<tr>
<td>vertigo</td>
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<tr>
<td><strong>Cardiac disorders</strong></td>
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<tr>
<td>heart failure</td>
<td></td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
<td></td>
</tr>
<tr>
<td>bladder cancer</td>
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1: visual disturbance2: macular oedema3: heart failure
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<tr>
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<td>flatulence</td>
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<th>Skin and subcutaneous tissue disorders</th>
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<td>sweating</td>
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<tr>
<th>Musculoskeletal and connective tissue disorders</th>
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<tbody>
<tr>
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<tbody>
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<td>glycosuria</td>
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<td>proteinuria</td>
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1 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.

2 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.

3 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. Heart failure has been reported rarely with marketing use of pioglitazone, but more frequently when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure.

4 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%).

5 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.

6 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.

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

Hypoglycaemia may occur in combination with sulphonylureas or insulin. 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.

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

Fasting and postprandial glycaemic control is improved in patients with type 2 diabetes mellitus. The improved glycaemic control is associated with a reduction in both fasting and postprandial plasma insulin concentrations. A clinical trial of pioglitazone vs. gliclazide as monotherapy was extended to two years in order to assess time to treatment failure (defined as appearance of 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 a stroke. Approximately half of the study population had at least two of the cardiovascular history entry criteria. Almost all subjects (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors, angiotensin II antagonists, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates).

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

### 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.

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

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

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

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. Fetal 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 fetal 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: no environmental impact is anticipated from the clinical use of Pioglitazone.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose Monohydrate
Hydroxypropyl Cellulose
6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
1. Cold form blister pack comprises of oriented polyamide+ aluminium foil+ PVC film with the backing of hard tempered, aluminium foil coated with heat sealed lacquer on inner side.

Pack sizes (for all strengths): 14, 28, 30, 50, 56, 84, 90 and 98 tablets

2. Desiccant embedded cold form blister pack comprises of oriented polyamide, aluminium foil, PE + desiccant, HDPE coating with the lidding foil laminate (aluminium foil, heat seal extrusion coating)

Pack sizes (for all strengths): 14, 28, 30, 50, 56, 84, 90 and 98 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
RANBAXY (UK) LIMITED
BUILDING 4, CHISWICK PARK
566 CHISWICK HIGH ROAD
LONDON
W4 5YE

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0657

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/03/2012

10 DATE OF REVISION OF THE TEXT
22/03/2012
Module 3
Product Information Leaflets
Please note that there is no mock-up available. The marketing authorisation holder has stated that it does not intend to market the product; therefore no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL to the regulatory authority for review before marketing the product.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pioglitazone 15mg, 30mg, 45mg Tablets
pioglitazone

Read all of this leaflet carefully before you start taking this medicine.

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

In this leaflet:

1. What Pioglitazone Tablets are and what are they used for
2. Before you take Pioglitazone Tablets
3. How to take Pioglitazone Tablets
4. Possible side effects
5. Storing Pioglitazone Tablets
6. Further information

1. WHAT PIOGLITAZONE TABLETS ARE AND WHAT ARE THEY USED FOR

Pioglitazone 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.

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

Pioglitazone tablets 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. BEFORE YOU TAKE PIOGLITAZONE TABLETS

Do not take Pioglitazone tablets

- If you are hypersensitive (allergic) to pioglitazone or any of the other ingredients of Pioglitazone Tablets.
- If you have heart failure or have had heart failure in the past.
- If you have liver disease.
- If you suffer from diabetic ketoacidosis (a complication of diabetes causing rapid weight loss, nausea or vomiting).
- If you have or have ever had bladder cancer
• If you have blood in your urine that your doctor has not checked.

**Take special care with Pioglitazone Tablets:**

Tell your doctor before you start to take this medicine.

• If you retain water (fluid retention) or have heart failures problems in particular if you are over 75 years old.
• If you have a special type of diabetic eye disease called macular oedema (swelling of the back of the eye).
• If you have a problem with your liver or heart. Before you start taking Pioglitazone Tablets 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 Pioglitazone Tablets 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 have cysts on your ovaries (polycystic ovary syndrome). There may be an increased possibility of becoming pregnant because you may ovulate again when you take Pioglitazone Tablets. If this applies to you, use appropriate contraception to avoid the possibility of an unplanned pregnancy.

If you take Pioglitazone Tablets 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 women (but not in men) taking pioglitazone. Your doctor will take this into account when treating your diabetes.

**Children**
Use in children under 18 years is not recommended.

**Taking other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription.

You can usually continue to take other medicines whilst you are being treated with Pioglitazone Tablets. However, certain medicines are especially likely to affect the amount of sugar in your blood:
• Gemfibrozil (used to lower cholesterol)
• Rifampicin (used for treatment of 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 Pioglitazone may need to be changed.
Taking Pioglitazone Tablets 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
Tell your doctor if
- you are, you think you might be or are planning to become pregnant.
- you are breast-feeding or if you are planning to breast-feed your baby
Your doctor will advise you to discontinue this medicine.

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

Important information about some of the ingredients of Pioglitazone Tablets:
This medicinal product contains lactose monohydrate. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking Pioglitazone Tablets

3. HOW TO TAKE PIOGLITAZONE TABLETS

One tablet of 15 mg, 30 mg or 45 mg 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 Pioglitazone Tablets is too weak, talk to your doctor.

When Pioglitazone Tablets are 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 Pioglitazone Tablets. 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 Pioglitazone Tablets.

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

If you take more Pioglitazone Tablets than you should:
If you accidentally take too many tablets, or if someone else or a child takes your medicine, talk to a doctor or pharmacist immediately. Your blood sugar could fall below the normal level 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 Pioglitazone Tablets:
Take Pioglitazone 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 Pioglitazone Tablets
Pioglitazone Tablets should be used every day to work properly. If you stop taking Pioglitazone 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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Pioglitazone Tablets can cause some side effects, although not everyone gets them.

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

Heart failure has been experienced commonly (1 to 10 users in 100) in patients taking Pioglitazone 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 (1 to 10 users in 1000) in patients taking Pioglitazone. 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 Pioglitazone in combination with insulin. If you experience this side effect, talk to your doctor as soon as possible.

Broken bones have been reported commonly (1 to 10 users in 100) in women patients taking Pioglitazone. 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 Pioglitazone. 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.

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

common (affects 1 to 10 users in 100)
  - weight gain
  - respiratory infection
  - numbness
  - abnormal vision

uncommon (affects 1 to 10 users in 1,000)
  - inflammation of the sinuses (sinusitis)
- difficulty sleeping (insomnia)

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

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

very common (affects more than 1 user in 10)
- decreased blood sugar (hypoglycaemia)

common (affects 1 to 10 users in 100)
- headache
- dizziness
- flatulence
- joint pain
- impotence
- small reduction in red blood cell count
- back pain
- shortness of breath

uncommon (affects 1 to 10 users in 1,000)
- spinning sensation (vertigo)
- sweating
- tiredness
- sugar in urine, proteins in urine
- increased appetite
- increase in enzymes

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

5. **HOW TO STORE PIOGLITAZONE TABLETS**

Keep out of the reach of children.

Do not use Pioglitazone tablets after the expiry date which is stated on the blister and the carton after {Exp}. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
6. FURTHER INFORMATION

What Pioglitazone Tablets contains

The active substance is Pioglitazone.

The other ingredients are lactose monohydrate, hydroxypropyl cellulose, carmellose calcium, purified water, magnesium stearate.

What Pioglitazone Tablets look like and contents of the pack

**Pioglitazone 15mg:** The tablets are white to off white, round of about 5.0 mm diameter, flat beveled edge tablet, debossed with 'RB' on one side and '94' on the other side.

**Pioglitazone 30mg:** The tablets are white to off white, round of about 7.0 mm diameter, flat beveled edge tablet, debossed with 'RB' on one side and '95' on the other side.

**Pioglitazone 45mg:** The tablets are white to off white, round of about 8.0 mm diameter, flat beveled edge tablet, debossed with 'RB' on one side and '96' on the other side.

Product is available in following pack sizes.

(For 15mg, 30mg and 45mg strength)

Cold from blister with 14, 28, 30, 50, 56, 84, 90 and 98 tablets
Desiccant Embedded Cold form blister with 14, 28, 30, 50, 56, 84, 90 and 98 tablets

Not all pack sizes may be marketed

Marketing Authorization Holder:

[To be completed nationally]

Manufacturer:

**Ranbaxy Ireland Ltd.** Spafield, Cork Road, Cashel, Co. Tipperary, Ireland

**Basics GmbH,** Hemmelrather Weg 201, D-51377 Leverkusen, Germany

**Terapia SA,** 124 Fabricii Street, 400 632 Chui Napoca, Romania
Module 4
Labelling

Please note that there is no mock-up available. The marketing authorisation holder has stated that it does not intend to market the product; therefore, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK labelling to the regulatory authority for review before marketing the product.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

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1. **NAME OF THE MEDICINAL PRODUCT**

Pioglitazone 15 mg Tablets
Pioglitazone 30 mg Tablets
Pioglitazone 45 mg Tablets

*pioglitazone*

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 16.53 mg Pioglitazone Hydrochloride, equivalent to 15 mg of pioglitazone.
Each tablet contains 33.06 mg Pioglitazone Hydrochloride, equivalent to 30 mg of pioglitazone.
Each tablet contains 49.59 mg Pioglitazone Hydrochloride, equivalent to 45 mg of pioglitazone.

3. **LIST OF EXCIPIENTS**

This medicinal product contains lactose, see package information leaflet for more information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Tablets

| 14 tablets |
| 28 tablets |
| 30 tablets |
| 50 tablets |
| 56 tablets |
| 84 tablets |
| 90 tablets |
| 98 tablets |

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use only
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**
8. **EXPIRY DATE**

Exp.: 

9. **SPECIAL STORAGE CONDITIONS**

No special storage condition required

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**

[To be completed nationally]

12. **MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

13. **MANUFACTURER'S BATCH NUMBER**

B. N.

14. **GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Pioglitazone 15 mg Tablets
Pioglitazone 30 mg Tablets
Pioglitazone 45 mg Tablets
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Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the relevant member states considered that the applications for Pioglitazone 15 mg, 30 mg and 45 mg Tablets (PL 14894/0655-7; UK/H/3548/001-3/DC) could be approved. These applications were submitted by the decentralised procedure, with the UK as reference member state (RMS) and the following as concerned member states (CMS) in the respective procedures:
- UK/H/3548/001/DC: France (FR), Portugal (PT) and Romania (RO)
- UK/H/3548/002/DC: France (FR), the Netherlands (NL), Portugal (PT) and Romania (RO)
- UK/H/3548/003/DC: Portugal (PT) and Romania (RO).

Pioglitazone 15 mg, 30 mg and 45 mg Tablets are prescription only medicines (POM) and are indicated as second or third line 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 adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

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.

These applications for Pioglitazone 15 mg, 30 mg and 45 mg Tablets were submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Actos 15 mg, 30 mg and 45 mg Tablets, granted via the centralised procedure in the member states (including the UK) to Takeda Global Research and Development Centre (Europe) Limited since October 2000.
Pioglitazone hydrochloride is a thiazolidinedione and a potent and highly selective agonist for the nuclear receptor peroxisome proliferator-activated receptor (PPAR)γ. PPARγ receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ receptors modulate the transcription of a number of insulin-responsive genes involved in the control of glucose and lipid metabolism. This results in an enhancement of insulin sensitivity, which manifests in reduced hepatic glucose production, increased glucose uptake in muscle, and reduced lipolysis in adipocytes. As a result of these interactions, pioglitazone treatment is associated with clinically relevant metabolic improvements of fasting and postprandial glycaemic control in patients with type 2 diabetes mellitus.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for these applications as the pharmacology of pioglitazone hydrochloride is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Pioglitazone 15mg Tablets  
Pioglitazone 30mg Tablets  
Pioglitazone 45mg Tablets |
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<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Pioglitazone hydrochloride</td>
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</table>
| Pharmacotherapeutic classification (ATC code)      | Drugs used in diabetes, blood glucose lowering drugs; excl.insulins  
ATC code: A10BG03.                                    |
| Pharmaceutical form and strength(s)               | 15mg Tablets  
30mg Tablets  
45mg Tablets                                        |
| Reference numbers for the Decentralised Procedure | UK/H/3548/001/DC  
UK/H/3548/002/DC  
UK/H/3548/003/DC                                      |
| Reference Member State                            | United Kingdom (UK)                              |
| Member States concerned                           | UK/H/3548/001/DC: France (FR), Portugal (PT) and Romania (RO)  
UK/H/3548/002/DC: France (FR), the Netherlands (NL), Portugal (PT) and Romania (RO)  
UK/H/3548/003/DC: Portugal (PT) and Romania (RO) |
| Marketing Authorisation Number(s)                 | PL 14894/0655  
PL 14894/0656  
PL 14894/0657                                         |
| Name and address of the authorisation holder       | Ranbaxy (UK) Limited  
Building 4,  
Chiswick Park,  
566 Chiswick High Road,  
London  
United Kingdom.                                    |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S.  Active substance

INN/Ph.Eur name:  Pioglitazone hydrochloride

Chemical name:
(5RS)-5-[4-(2-(5-ethylpyridin-2-yl)ethoxy]benzyl]-1,3-thiazolidine-2, 4-dione hydrochloride

Structure:

Physical form:  White or off white powder.
Solubility:  Slightly soluble in methanol, insoluble in water.

Molecular formula:  C₁₉H₂₁ClN₂O₃S
Molecular weight:  392.9

Pioglitazone hydrochloride complies with in-house specifications.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines.

Stability studies have been performed with the active substance and no significant changes of the parameters were observed. On the basis of the results, a suitable re-test period could be approved.
P. Medicinal Product
Other Ingredients
Other ingredients in the tablet core consist of pharmaceutical excipients lactose monohydrate, hydroxypropyl cellulose, carmelllose calcium and magnesium stearate.

All excipients comply with their respective European Pharmacopoeia monographs.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. Confirmation has been provided that the magnesium stearate used is of vegetable origin. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to produce safe, efficacious products containing pioglitazone hydrochloride that could be considered generic medicinal products of Actos 15 mg, 30 mg and 45 mg Tablets.

The applicant has provided suitable product development sections. Valid justifications for the use and amounts of each excipient have been provided.

Comparative in vitro dissolution profiles have been provided for the proposed and reference products. An impurity study was conducted, but did not involve the reference product.

The reference product used in the bioequivalence study is Actos 45 mg Tablets, licensed in the UK to Takeda Global Research and Development Centre (Europe) Limited.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on pilot-scale batches of each strength have been provided and are satisfactory. The applicant has committed to perform process validation on future commercial-scale batches.

Finished Product Specification
The finished product specifications are acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.
Container-Closure System
These products are packaged in the following containers:

i) Cold form blister packs comprised of oriented polyamide, aluminium film and polyvinyl chloride (PVC) with the backing of hard tempered, aluminium foil coated with heat sealed lacquer on the inner side.

ii) Dessicant embedded cold form blister pack comprised of oriented polyamide, aluminium foil, polyethylene and dessicant, high density polyethylene (HDPE) coating with the lidding foil laminate (aluminium foil, heat seal extrusion coating).

The products come in the following pack sizes:
Cold form blister pack: 14, 28, 30, 50, 56, 84, 90 and 98 tablets
Dessicant embedded cold form blister pack: 14, 28, 30, 50, 56, 84, 90 and 98 tablets

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with the relevant EU directives and EU legislation regarding contact with food.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support an adequate shelf-life of 24 months with no special storage instructions.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically acceptable. The UK approved SmPCs, PIL and labelling (text only) are included in modules 2, 3 and 4 of this report.

User testing results have been submitted for the PIL for this product. The results indicate that the PIL is in accordance with Article 59 of Council Directive 2001/83/EC, as amended and is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of pioglitazone hydrochloride are well-known. As pioglitazone hydrochloride is a widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required. An overview based on literature is therefore appropriate.

Non-Clinical Overview
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Environmental Risk Assessment
A satisfactory justification has been provided for the absence of an Environmental Risk Assessment.

Conclusion
From a non-clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.3 CLINICAL ASPECTS

Clinical Pharmacology

With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required.

Pharmacokinetics

Bioequivalence study

An open-label, single-dose, balanced, randomised, two-period, two-sequence, two-treatment, crossover study to compare the pharmacokinetics of the test product Pioglitazone 45 mg Tablets versus the reference product Actos 45 mg Tablets (pioglitazone hydrochloride) in healthy subjects under fasted conditions.

Blood samples were taken pre- and up to 120 hours post dose. The washout period between each treatment period was 17 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for pioglitazone hydrochloride are presented below as log-tranformed values for geometric means:

<table>
<thead>
<tr>
<th>Pioglitazone hydrochloride</th>
<th>Treatment</th>
<th>AUC₀⁻ᵗ (ng.h/mL)</th>
<th>AUC₀⁻∞ (ng.h/mL)</th>
<th>Cₘₐₓ (ng/mL)</th>
</tr>
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<tbody>
<tr>
<td>Test (T)</td>
<td>18561.77483</td>
<td>18869.16478</td>
<td>1666.124</td>
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<tr>
<td>Reference (R)</td>
<td>17715.83976</td>
<td>18022.69400</td>
<td>1562.239</td>
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<tr>
<td>T/R Ratio</td>
<td>106.69</td>
<td>106.36</td>
<td>110.21</td>
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<td>(90% CI)</td>
<td>(100.57 – 113.17)</td>
<td>(100.37 – 112.70)</td>
<td>(101.59 – 119.57)</td>
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AUC₀⁻ᵗ area under the plasma concentration-time curve from time zero to infinity
AUC₀⁻∞ area under the plasma concentration-time curve from time zero to t hours
Cₘₐₓ maximum plasma concentration

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC₀⁻ᵗ and Cₘₐₓ for pioglitazone hydrochloride lie within acceptable limits (80-125%). Thus, bioequivalence has been shown between the test and reference products in this study.

As the product range meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) for a biowaiver for the other strengths, the results and conclusions of the bioequivalence study on the 45 mg strength can be extrapolated to Pioglitazone 15 mg and 30 mg Tablets.

Efficacy

No new efficacy data were submitted with these generic applications and none were required.
Safety
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with these generic applications and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

The Pharmacovigilance System and Risk Management Plan
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory justification has been provided for the absence of a Risk Management Plan.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are clinically satisfactory and consistent with those for the reference products, where appropriate.

Clinical Overview
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA Forms
The MAA forms are clinically satisfactory.

Conclusions
From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Pioglitazone 15 mg, 30 mg and 45 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Pioglitazone 45 mg Tablets and the reference product Actos 45 mg Tablets. These bioequivalence study results and conclusions can be extrapolated to Pioglitazone 15 mg and 30 mg Tablets.

No new or unexpected safety concerns arose from the bioequivalence study.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with pioglitazone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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