Public Assessment Report

Decentralised Procedure

PIOGLITAZONE INTAS 15MG TABLETS
PIOGLITAZONE INTAS 30MG TABLETS
PIOGLITAZONE INTAS 45MG TABLETS

(Pioglitazone hydrochloride)

Procedure No: UK/H/4844/001-3/DC

UK Licence No: PL 30139/0028-30

INTAS PHARMACEUTICALS LIMITED.
LAY SUMMARY

On 22 February 2012, Greece, Spain, Italy, Poland and the UK agreed to grant Marketing Authorisations to Intas Pharmaceuticals Limited for the medicinal products Pioglitazone Intas 15mg, 30mg and 45mg tablets (PL 30139/0028-30; UK/H/4844/001-3/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 01 May 2012. These are Prescription-Only Medicines (POM).

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

Pioglitazone Intas 15mg, 30mg and 45mg tablets can be used in different ways:

- It 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.
- It may be added to other therapies (such as metformin, sulfonylurea or insulin) which have failed to provide sufficient control in blood sugar.

No new or unexpected safety concerns arose from these applications and it was judged that the benefits of taking Pioglitazone Intas 15mg, 30mg and 45mg tablets outweigh the risks and therefore Marketing Authorisations were granted.
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# Module 1

| Product Name       | Pioglitazone Intas 15mg tablets  
|                   | Pioglitazone Intas 30mg tablets  
|                   | Pioglitazone Intas 45mg tablets  |
| Type of Application| Generic, Article 10.1            |
| Active Substances  | Pioglitazone hydrochloride       |
| Form               | Tablets                          |
| Strength           | 15 mg, 30 mg and 45 mg.          |
| MA Holder          | Intas Pharmaceuticals Limited, Sage house, 319, Pinner Road, North Harrow, Middlesex HA1 4HF, UK. |
| Reference Member State (RMS) | UK                           |
| Concerned Member State (CMS) | UK/H/4844/01-2/DC: Greece, Spain, Italy and Poland |
| Procedure Number   | UK/H/4844/001-3/DC               |
| Timetable          | Day 210– 22 February 2012.      |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Pioglitazone Intas 15mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 15 mg of pioglitazone as hydrochloride.
Excipient(s): 37.24 mg of lactose monohydrate
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White to off white, round, biconvex, uncoated tablets debossed with ‘P’ on one side and ‘15’ on 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 section 4.3 and 4.4).

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

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

4.3 Contraindications
Pioglitazone is contraindicated in patients with:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- cardiac failure or history of cardiac failure (NYHA stages I to IV)
- hepatic impairment
- diabetic ketoacidosis
- current bladder cancer or a history of bladder cancer
- uninvestigated macroscopic haematuria

4.4 Special warnings and precautions for use
Fluid retention and cardiac failure:
Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction or symptomatic coronary artery disease or the elderly), physicians should start with the lowest available dose and increase the dose gradually. Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with reduced cardiac reserve. There have been post-marketing cases of cardiac failure reported when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure. Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin. Since insulin and pioglitazone are 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, the medicinal product should be discontinued.

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

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

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

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

**Others:**
An increased incidence in bone fractures in women was seen in a pooled analysis of adverse reactions of bone fracture from randomised, controlled, double blind clinical trials in over 8100 pioglitazone and 7400 comparator treated patients, on treatment for up to 3.5 years.
Fractures were observed in 2.6% of women taking pioglitazone compared to 1.7% of women treated with a comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%). The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this dataset on pioglitazone is therefore 0.8 fractures per 100 patient years of use.

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

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. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth. The relevance of such a mechanism in humans is unclear and pioglitazone should not be used in pregnancy.

Breast-feeding:

Pioglitazone has been shown to be present in the milk of lactating rats. It is not known whether pioglitazone is secreted in human milk. Therefore, pioglitazone should not be administered to breast-feeding women.

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

4.7 Effects on ability to drive and use machines
Pioglitazone Hydrochloride tablet 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 (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing incidence and seriousness.

<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 with metformin</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>uncommon</td>
</tr>
<tr>
<td>sinusitis</td>
<td>common</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>uncommon</td>
</tr>
<tr>
<td>appetite increased</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</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></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>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
</tr>
<tr>
<td>vertigo</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorder</td>
<td></td>
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<tr>
<td>heart failure³</td>
<td></td>
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<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
<td></td>
</tr>
<tr>
<td>bladder cancer</td>
<td>uncommon</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
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<tr>
<td>dyspnœa</td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>flatulence</td>
<td>uncommon</td>
</tr>
<tr>
<td>Adverse reaction</td>
<td>Frequency of adverse reactions of pioglitazone by treatment regimen</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Monotherapy</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
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<tr>
<td>sweating</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal system and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>fracture bone&lt;sup&gt;3&lt;/sup&gt;</td>
<td>common</td>
</tr>
<tr>
<td>arthralgia</td>
<td>common</td>
</tr>
<tr>
<td>back pain</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
</tr>
<tr>
<td>haematuria</td>
<td>common</td>
</tr>
<tr>
<td>glycosuria</td>
<td>uncommon</td>
</tr>
<tr>
<td>proteinuria</td>
<td>uncommon</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
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<tr>
<td>erectile dysfunction</td>
<td>common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>oedema</td>
<td></td>
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<tr>
<td>fatigue</td>
<td></td>
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<tr>
<td>Investigations</td>
<td></td>
</tr>
<tr>
<td>weight increased&lt;sup&gt;4&lt;/sup&gt;</td>
<td>common</td>
</tr>
<tr>
<td>blood creatine phospho-kinase increased</td>
<td></td>
</tr>
<tr>
<td>increased lactic dehydro-genase</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased&lt;sup&gt;4&lt;/sup&gt;</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%).

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.

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: A10 BG 03.
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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with
Pioglitazone Hydrochloride tablet in all subsets of the paediatric population in Type 2 Diabetes
Mellitus. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration, pioglitazone is rapidly absorbed, and peak plasma concentrations of
unchanged pioglitazone are usually achieved 2 hours after administration. Proportional increases of
the plasma concentration were observed for doses from 2 – 60 mg. Steady state is achieved after 4–7
days of dosing. Repeated dosing does not result in accumulation of the compound or metabolites.
Absorption is not influenced by food intake. Absolute bioavailability is greater than 80 %.

Distribution:

The estimated volume of distribution in humans is 0.25 l/kg.
Pioglitazone and all active metabolites are extensively bound to plasma protein (> 99 %).

Biotransformation:

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

In vitro studies have shown no evidence that pioglitazone inhibits any subtype of cytochrome P450.
There is no induction of the main inducible P450 isoenzymes 1A, 2C8/9, and 3A4 in man.
Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Concomitant administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) or with rifampicin (an inducer of cytochrome P450 2C8) is reported to increase or decrease, respectively, the plasma concentration of pioglitazone (see section 4.5).

Elimination:

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

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. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth.

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

The formation and presence of urinary calculi with subsequent irritation and hyperplasia was postulated as the mechanistic basis for the observed tumourigenic response in the male rat. A 24-month mechanistic study in male rats demonstrated that administration of pioglitazone resulted in an increased incidence of hyperplastic changes in the bladder. Dietary acidification significantly decreased but did not abolish the incidence of tumours. The presence of microcrystals exacerbated the hyperplastic response but was not considered to be the primary cause of hyperplastic changes. The relevance to humans of the tumourigenic findings in the male rat cannot be excluded.

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Carmellose calcium
Hydroxypropyl cellulose
Lactose monohydrate
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

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

6.5 Nature and contents of container
Aluminium/aluminium blisters, packs of 14, 28, 30, 50, 56, 84, 90, 98, 112 and 196 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Intas Pharmaceuticals Limited,
Sage house, 319, Pinner Road,
North Harrow, Middlesex HA1 4HF,
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 30139/0028

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/05/2012

10 DATE OF REVISION OF THE TEXT
01/05/2012
1 NAME OF THE MEDICINAL PRODUCT
Pioglitazone Intas 30mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 30 mg of pioglitazone as hydrochloride.
Excipient(s): 74.46 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White to off white, flat, round uncoated tablets with beveled edges debossed with ‘PIO’ on one side and ‘30’ 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 section 4.3 and 4.4).

**Paediatric population**

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

**Method of administration**

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

### 4.3 Contraindications
Pioglitazone is contraindicated in patients with:

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

### 4.4 Special warnings and precautions for use

**Fluid retention and cardiac failure:**

Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction or symptomatic coronary artery disease or the elderly), physicians should start with the lowest available dose and increase the dose gradually. Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with reduced cardiac reserve. There have been post-marketing cases of cardiac failure reported when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure. Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin. Since insulin and pioglitazone are 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, the medicinal product should be discontinued.

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

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

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

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

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

Fractures were observed in 2.6% of women taking pioglitazone compared to 1.7% of women treated with a comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).
The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this dataset on pioglitazone is therefore 0.8 fractures per 100 patient years of use.

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

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. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth. The relevance of such a mechanism in humans is unclear and pioglitazone should not be used in pregnancy.

Breast-feeding:
Pioglitazone has been shown to be present in the milk of lactating rats. It is not known whether pioglitazone is secreted in human milk. Therefore, pioglitazone should not be administered to breast-feeding women.

Fertility
In animal fertility studies there was no effect on copulation, impregnation or fertility index.
4.7 Effects on ability to drive and use machines
Pioglitazone Hydrochloride tablets 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 (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing incidence and seriousness.

<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><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></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>
<td></td>
</tr>
<tr>
<td>hypo-glycaemia</td>
<td></td>
</tr>
<tr>
<td>appetite increased</td>
<td></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></td>
</tr>
<tr>
<td>dizziness</td>
<td></td>
</tr>
<tr>
<td>insomnia</td>
<td>uncommon</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>visual disturbance^1</td>
<td>common</td>
</tr>
<tr>
<td>macular oedema^2</td>
<td>not known</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
</tr>
<tr>
<td>vertigo</td>
<td></td>
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<tr>
<td><strong>Cardiac disorder</strong></td>
<td></td>
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<tr>
<td>heart failure^3</td>
<td></td>
</tr>
<tr>
<td><strong>Neoplasms benign, malignant and unspecified (including cysts and polyps)</strong></td>
<td></td>
</tr>
<tr>
<td>Adverse reaction</td>
<td>Frequency of adverse reactions of pioglitazone by treatment regimen</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Monotherapy with metformin</td>
</tr>
<tr>
<td>bladder cancer</td>
<td>uncommon</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>dyspnoea</td>
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</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>flatulence</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>sweating</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal system and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>fracture bone(^1)</td>
<td>common</td>
</tr>
<tr>
<td>arthralgia</td>
<td>common</td>
</tr>
<tr>
<td>back pain</td>
<td></td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>haematuria</td>
<td>common</td>
</tr>
<tr>
<td>glycosuria</td>
<td></td>
</tr>
<tr>
<td>proteinuria</td>
<td></td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td></td>
</tr>
<tr>
<td>erectile dysfunction</td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>oedema</td>
<td></td>
</tr>
<tr>
<td>fatigue</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>weight increased(^2)</td>
<td>common</td>
</tr>
<tr>
<td>blood creatine phospho-kinase increased</td>
<td></td>
</tr>
<tr>
<td>increased lactic dehydro-genase</td>
<td></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.
Oedema was reported in 6-9% of patients treated with pioglitazone over one year in controlled clinical trials. The oedema rates for comparator groups (sulphonylurea, metformin) were 2 – 5%. The reports of oedema were generally mild to moderate and usually did not require discontinuation of treatment.

In 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.

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%).

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.

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: A10 BG 03.

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 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.

**Paediatric population**

The European Medicines Agency has waived the obligation to submit the results of studies with Pioglitazone Hydrochloride tablets in all subsets of the paediatric population in Type 2 Diabetes Mellitus. See section 4.2 for information on paediatric use.

### 5.2 Pharmacokinetic properties

**Absorption:**

Following oral administration, pioglitazone is rapidly absorbed, and peak plasma concentrations of unchanged pioglitazone are usually achieved 2 hours after administration. Proportional increases of
the plasma concentration were observed for doses from 2 – 60 mg. Steady state is achieved after 4–7 days of dosing. Repeated dosing does not result in accumulation of the compound or metabolites.

Absorption is not influenced by food intake. Absolute bioavailability is greater than 80 %.

**Distribution:**
The estimated volume of distribution in humans is 0.25 l/kg. Pioglitazone and all active metabolites are extensively bound to plasma protein (> 99 %).

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

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

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

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

**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. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth.

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

The formation and presence of urinary calculi with subsequent irritation and hyperplasia was postulated as the mechanistic basis for the observed tumorigenic 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 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
Carmellose calcium
Hydroxypropyl cellulose
Lactose monohydrate
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
4 years

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

6.5 Nature and contents of container
Aluminium/aluminium blisters, packs of 14, 28, 30, 50, 56, 84, 90, 98, 112 and 196 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Intas Pharmaceuticals Limited,
Sage house, 319, Pinner Road,
North Harrow, Middlesex HA1 4HF,
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 30139/0029

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/05/2012

10 DATE OF REVISION OF THE TEXT
01/05/2012
1 NAME OF THE MEDICINAL PRODUCT
Pioglitazone Intas 45mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 45 mg of pioglitazone as hydrochloride.
Excipient(s): 111.70 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White to off white, flat, round uncoated tablets with beveled edges debossed with ‘PIO’ on one side and ‘45’ 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 section 4.3 and 4.4).

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

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

### 4.3 Contraindications
Pioglitazone is contraindicated in patients with:

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

### 4.4 Special warnings and precautions for use

**Fluid retention and cardiac failure:**
Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction or symptomatic coronary artery disease or the elderly), physicians should start with the lowest available dose and increase the dose gradually. Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with reduced cardiac reserve. There have been post-marketing cases of cardiac failure reported when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure. Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin. Since insulin and pioglitazone are 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, the medicinal product should be discontinued.

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

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

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

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

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

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

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

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

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. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth. The relevance of such a mechanism in humans is unclear and pioglitazone should not be used in pregnancy.

Breast-feeding:
Pioglitazone has been shown to be present in the milk of lactating rats. It is not known whether pioglitazone is secreted in human milk. Therefore, pioglitazone should not be administered to breast-feeding women.

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

4.7 Effects on ability to drive and use machines
Pioglitazone Hydrochloride tablet 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 (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing incidence and seriousness.

<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 with metformin with sulphonylurea with metformin and Sulphonylurea with insulin</td>
</tr>
<tr>
<td></td>
<td>Combination</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>uncommon</td>
</tr>
<tr>
<td>appetite increased</td>
<td>uncommon</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>common</td>
</tr>
<tr>
<td>dizziness</td>
<td>common</td>
</tr>
<tr>
<td>insomnia</td>
<td>uncommon</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>visual disturbance</td>
<td>common</td>
</tr>
<tr>
<td>macular oedema</td>
<td>not known</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
</tr>
<tr>
<td>vertigo</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorder</td>
<td></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>
<td>uncommon</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
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<tr>
<td>dyspnoea</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>flatulence</td>
<td>uncommon</td>
</tr>
</tbody>
</table>

1. visual disturbance
2. macular oedema
3. heart failure
<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>Skin and subcutaneous tissue disorders</td>
<td>sweating</td>
</tr>
<tr>
<td>Musculoskeletal system and connective tissue disorders</td>
<td>fracture bone&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>arthralgia</td>
</tr>
<tr>
<td></td>
<td>back pain</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>haematuria</td>
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<tr>
<td></td>
<td>glycosuria</td>
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<tr>
<td></td>
<td>proteinuria</td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td>erectile dysfunction</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>oedema</td>
</tr>
<tr>
<td></td>
<td>fatigue</td>
</tr>
<tr>
<td>Investigations</td>
<td>weight increased&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>blood creatine phospho-kinase increased</td>
</tr>
<tr>
<td></td>
<td>increased lactic dehydro-genase</td>
</tr>
<tr>
<td></td>
<td>Alanine aminotransferase increased&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup>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.

<sup>2</sup>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.

<sup>3</sup>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.
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%).

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.

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: A10 BG 03.
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 one year clinical trials, 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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Pioglitazone Hydrochloride tablet in all subsets of the paediatric population in Type 2 Diabetes Mellitus. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption:
Following oral administration, pioglitazone is rapidly absorbed, and peak plasma concentrations of unchanged pioglitazone are usually achieved 2 hours after administration. Proportional increases of the plasma concentration were observed for doses from 2 – 60 mg. Steady state is achieved after 4–7 days of dosing. Repeated dosing does not result in accumulation of the compound or metabolites. Absorption is not influenced by food intake. Absolute bioavailability is greater than 80%.

Distribution:
The estimated volume of distribution in humans is 0.25 l/kg.
Pioglitazone and all active metabolites are extensively bound to plasma protein (> 99%).

Biotransformation:
Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 although other isoforms may be involved to a lesser degree. Three of the six identified metabolites are active (M-II, M-III, and M-IV). When activity, concentrations and protein binding are taken into account, pioglitazone and metabolite M-III contribute equally to efficacy. On this basis M-IV contribution to efficacy is approximately three-fold that of pioglitazone, whilst the relative efficacy of M-II is minimal.
In vitro studies have shown no evidence that pioglitazone inhibits any subtype of cytochrome P450. There is no induction of the main inducible P450 isoenzymes 1A, 2C8/9, and 3A4 in man.

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

Elimination:

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

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. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth.

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

The formation and presence of urinary calculi with subsequent irritation and hyperplasia was postulated as the mechanistic basis for the observed tumourigenic response in the male rat. A 24-month mechanistic study in male rats demonstrated that administration of pioglitazone resulted in an increased incidence of hyperplastic changes in the bladder. Dietary acidification significantly decreased but did not abolish the incidence of tumours. The presence of microcrystals exacerbated the hyperplastic response but was not considered to be the primary cause of hyperplastic changes. The relevance to humans of the tumourigenic findings in the male rat cannot be excluded.

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

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

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Carmellose calcium
Hydroxypropyl cellulose
Lactose monohydrate
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
4 years

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

6.5 Nature and contents of container
Aluminium/aluminium blisters, packs of 14, 28, 30, 50, 56, 84, 90, 98, 112 and 196 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local
requirements.

7 MARKETING AUTHORISATION HOLDER
Intas Pharmaceuticals Limited,
Sage house, 319, Pinner Road,
North Harrow, Middlesex HA1 4HF,
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 30139/0030

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/05/2012

10 DATE OF REVISION OF THE TEXT
01/05/2012
Module 3
The following text is the approved Patient Information Leaflet (PIL) text as agreed during the decentralised procedure. No PIL mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the PIL mock-up has been obtained.

Package leaflet: Information for the user
Pioglitazone Intas 15mg tablets
Pioglitazone Intas 30mg tablets
Pioglitazone Intas 45mg tablets

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

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

What is in this leaflet
1. What Pioglitazone Intas tablet is and what it is used for
2. What you need to know before you take Pioglitazone Intas tablets
3. How to take Pioglitazone Intas tablets
4. Possible side effects
5. How to store Pioglitazone Intas tablets
6. Contents of the pack and other information

1. What Pioglitazone Intas tablet is and what it is used for
Pioglitazone Intas tablet contains pioglitazone. It is an anti-diabetic medicine used to treat type 2 (non-insulin dependent) diabetes mellitus when metformin is not suitable or has failed to work adequately. This is the diabetes that usually develops in adulthood.
Pioglitazone Intas tablets helps control the level of sugar in your blood when you have type 2 diabetes by helping your body make better use of the insulin it produces. Your doctor will check whether Pioglitazone Intas tablet is working 3 to 6 months after you start taking it.
Pioglitazone Intas 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 provided sufficient control in blood sugar.

2. What you need to know before you take Pioglitazone Intas tablets
Do not take Pioglitazone Intas tablets
- if you are allergic to pioglitazone or any of the other ingredients of this medicine (listed in section 6).
- if you have heart failure or have had heart failure in the past.
- if you have liver disease
- if you have had diabetic ketoacidosis (a complication of diabetes causing rapid weight loss, nausea or vomiting).
- if you have or have ever had bladder cancer.
- if you have blood in your urine that your doctor has not checked.

Warnings and precautions:
Talk to your doctor or pharmacist before taking Pioglitazone Intas tablets
- if you retain water (fluid retention) or have heart failure 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 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 Intas tablets. If this applies to you, use appropriate contraception to avoid the possibility of an unplanned pregnancy.
- if you have a problem with your liver or heart. Before you start taking Pioglitazone Intas 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 Intas 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).
PAR Pioglitazone Intas 15mg, 30mg and 45mg tablets

If you take Pioglitazone Intas 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 and adolescents
Use in children under 18 years is not recommended.

Other medicines and Pioglitazone Intas tablets
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
You can usually continue to take other medicines whilst you are being treated with Pioglitazone Intas tablets
However, certain medicines are especially likely to affect the amount of sugar in your blood:
- gemfibrozil (used to lower cholesterol)
- rifampicin (used to treat tuberculosis and other infections)
Tell your doctor or pharmacist if you are taking any of these. Your blood sugar will be checked, and your dose of Pioglitazone Intas tablets may need to be changed.

Pioglitazone Intas 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, breastfeeding and fertility:
Tell your doctor if
- you are, you think you might be or are planning to become pregnant.
- you are breastfeeding or if you are planning to breast-feed your baby.

Your doctor will advise you to discontinue this medicine.

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

Pioglitazone Intas tablets contain Lactose monohydrate:
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 Intas tablets.

3. How to take Pioglitazone Intas tablets

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
The recommended dose is one tablet of 15/30/45 mg of pioglitazone 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 Intas tablet is too weak, talk to your doctor.
When Pioglitazone Intas 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 Intas 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 Intas tablets.
Your weight should be checked at regular intervals; if your weight increases, inform your doctor.

If you take more Pioglitazone Intas 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 Intas tablets
Take Pioglitazone Intas 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 Intas tablets
Pioglitazone Intas tablets should be used every day to work properly. If you stop using Pioglitazone Intas tablets, your blood sugar may go up. Talk to your doctor before stopping this treatment.

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

4. Possible side effects

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

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

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

Bladder cancer has been experienced uncommonly (may affect up to 1 in 100 people) in patients taking Pioglitazone Intas tablets. 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 Intas tablets in combination with insulin. If you experience this side effect, talk to your doctor as soon as possible.

Broken bones have been reported commonly (may affect up to 1 in 10 people) in women patients taking Pioglitazone Intas tablets. 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 Intas tablets. 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 have been experienced by some patients taking Pioglitazone Intas tablets

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

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

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

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

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

- common (may affect up to 1 in 10 people)
  - headache
  - dizziness
  - joint pain
PAR Pioglitazone Intas 15mg, 30mg and 45mg tablets

- impotence
- back pain
- shortness of breath.
- small reduction in red blood cell count
- flatulence

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

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Pioglitazone Intas tablets

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date, which is stated on the 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.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pioglitazone Intas tablets contains

The active substance is pioglitazone.

Each tablet contains 15/30/45 mg of pioglitazone (as hydrochloride).

The other ingredients are:
Lactose monohydrate, Carmellose calcium, Hydroxypropyl cellulose (E 463), Magnesium stearate (E 572).

What Pioglitazone Intas tablets looks like and contents of the pack

15 mg: White to off white, round, biconvex, uncoated tablets debossed with ‘P’ on one side and ‘15’ on other side.
30 mg: White to off white, flat, round uncoated tablets with beveled edges debossed with ‘PIO’ on one side and ‘30’ on the other side.
45 mg: White to off white, flat, round uncoated tablets with beveled edges debossed with ‘PIO’ on one side and ‘45’ on the other side.

Pioglitazone Intas tablet is available in Aluminium/ Aluminium blister packs containing 14, 28, 30, 50, 56, 84, 90, 98, 112 and 196 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Intas Pharmaceuticals Limited,
Sage house, 319, Pinner Road,
North Harrow, Middlesex HA1 4HF,
UK

Manufacturer
Accord Healthcare Limited,
Sage house, 319, Pinner Road,
North Harrow, Middlesex HA1 4HF,
UK

BIOTON S.A.,
02-516 Warszawa, ul. Starościerska 5
Poland

This leaflet was last revised in 04/2012.
Module 4
Labelling

The following text is the approved labelling text as agreed during the decentralised procedure. No labelling mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the labelling mock-ups has been obtained.

| MINIMUM PARTICULARS TO APPEAR ON BLISTERS |
| {Alu/Alu blister} |

1. NAME OF THE MEDICINAL PRODUCT

<Invented name 15/30/45 mg tablets>
Pioglitazone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER
PARTICULARS TO APPEAR ON <THE OUTER PACKAGING>
{Carton}

1. NAME OF THE MEDICINAL PRODUCT

<Invented name 15/30/45 mg tablets>
Pioglitazone

2. STATEMENT OF ACTIVE SUBSTANCE (S)

15 mg: Each tablet contains 15 mg pioglitazone (as hydrochloride)
30 mg: Each tablet contains 30 mg pioglitazone (as hydrochloride)
45 mg: Each tablet contains 45 mg of pioglitazone (as hydrochloride)

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet
14 tablets
28 tablets
30 tablets
50 tablets
56 tablets
84 tablets
90 tablets
98 tablets
112 tablets
196 tablets

5. METHOD AND ROUTE (S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

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

EXP

9. SPECIAL STORAGE CONDITIONS

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

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally

12. MARKETING AUTHORISATION NUMBER (S)

To be completed nationally

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

To be completed nationally

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Invented name 15, 30, 45 mg tablets>
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Pioglitazone Intas 15mg, 30mg and 45mg tablets (PL 30139/0028-30; UK/H/4844/001-3/DC) could be approved. These applications were submitted via the decentralised procedure, with the UK as Reference Member State (RMS) and Greece, Spain, Italy and Poland as Concerned Member State (CMS). These products are prescription-only medicines (POM).

Pioglitazone Intas 15mg, 30mg and 45mg tablets 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 (see section 4.4 of SmPC).

These are abridged applications submitted under 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 (Takeda Global Research and Development Centre (Europe) Limited, UK), which were first authorised using the Centralised procedure in October 2000.

Pioglitazone is a thiazolidinedione and a potent and highly selective agonist for the nuclear receptor peroxisome proliferator-activated receptor (PPAR)γ. PPARγ are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ receptor modulates the transcription of a number of insulin-responsive genes involved in the control of glucose and lipid metabolism. This results in enhanced 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 are intended to be generic versions of the originator products that have been licensed for over 10 years.

One bioequivalence study (single dose) was submitted to support these applications, comparing the test product Pioglitazone Intas 45mg tablets (Intas Pharmaceuticals Limited) with the reference product Actos 45 mg Tablets (Takeda Global Research and Development Centre (Europe) Limited, UK).

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were for products that are intended to be generic versions of the originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 22 February 2012. After the subsequent national phase, the licences were granted in the UK on 01 May 2012.
# II. ABOUT THE PRODUCT

| **Name of the product in the Reference Member State** | Pioglitazone Intas 15mg tablets  
| Pioglitazone Intas 30mg tablets  
| Pioglitazone Intas 45mg tablets |
| **Name(s) of the active substance(s) (INN)** | Pioglitazone hydrochloride |
| **Pharmacotherapeutic classification (ATC code)** | Drugs used in diabetes, blood glucose lowering drugs; excluding insulins (A10 BG 03) |
| **Pharmaceutical form and strength(s)** | 15 mg, 30 mg and 45 mg tablets |
| **Reference numbers for the Mutual Recognition Procedure** | UK/H/4844/001-3/DC |
| **Reference Member State** | United Kingdom |
| **Concerned Member State** | UK/H/4844/01-2/DC: Greece, Spain, Italy and Poland  
| UK/H/4844/03/DC: Greece, Italy and Poland |
| **Marketing Authorisation Number(s)** | PL 30139/0028-30 |
| **Name and address of the authorisation holder** | Intas Pharmaceuticals Limited, Sage house, 319, Pinner Road, North Harrow, Middlesex HA1 4HF, UK. |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Pioglitazone hydrochloride
Chemical names: (±)-5-[[4-[2-(5-Ethyl-2-pyridinyl)-ethoxy]phenyl ] methyl ]-2,4-thiazolidinedione hydrochloride;
(±)-5-[p-[2-(ethyl-2-pyridyl)ethoxy benzyl]-2,4-thiazolidinedione hydrochloride

Structure:

\[
\begin{align*}
\text{\text{H}_3\text{C}} & \text{O} \\
\text{\text{N}} & \\
\text{O} & \\
\text{\text{S}} \text{NH} \cdot \text{HCl}
\end{align*}
\]

Molecular formula: \( C_{19}H_{20}N_2O_3S \cdot HCl \)
Molecular mass: 392.90
Appearance: Pioglitazone hydrochloride is a white to off-white crystalline powder.
Solubility: It is soluble in dimethyl formamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water and ether.

Pioglitazone hydrochloride is not the subject of a European Pharmacopoeia monograph.

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.

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.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

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

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.
P. Medicinal Product

Other Ingredients
Other ingredients consist of the pharmaceutical excipients carmellose calcium, hydroxypropyl cellulose, lactose monohydrate and magnesium stearate.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk 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 formulate stable, robust, tablets containing 15 mg, 30 mg or 45 mg pioglitazone, which could be considered generic medicinal products of Actos 15 mg, 30 mg and 45 mg Tablets (Takeda Global Research and Development Centre (Europe) Limited, UK).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale and has shown satisfactory results. In addition the Marketing Authorisation Holder (MAH) has committed to perform process validation on commercial scale batches for all strengths.

Finished Product Specification
The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
All strengths of the finished product are packaged in aluminium/aluminium blister strips in pack sizes of 14, 28, 30, 50, 56, 84, 90, 98, 112 and 196 tablets.

It has been stated that not all pack sizes may be marketed, however, the Marketing Authorisation Holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.
Stability of the product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years for the 15 mg strength and 4 years for the 30 mg and 45 mg strengths with no special storage conditions.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet 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.

Marketing Authorisation Application (MAA) form
The MAA forms are 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
There are no objections to the approval of these products from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of pioglitazone are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

Since Pioglitazone Intas 15mg, 30mg and 45mg tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment (ERA) is therefore not deemed necessary.

There are no objections to the approval of these products from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open label, randomised, single-dose, two-period, two-sequence, two treatment, crossover study to compare the pharmacokinetics of the test product Pioglitazone Intas 45mg tablets (Intas Pharmaceuticals Limited) versus the reference product Actos
45 mg Tablets (Takeda Global Research and Development Centre (Europe) Limited, UK) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 45 mg tablet administered after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 192 hours post dose. The washout period between treatment periods was at least 15 days.

The pharmacokinetic results for pioglitazone are presented below (log-transformed values; geometric least square mean and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>In-transformed Geometric Least Squares Mean (n=46)</th>
<th>90% Confidence Interval (Parametric)</th>
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<tbody>
<tr>
<td></td>
<td>Reference Product-A</td>
<td>Test Product-B</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1353.508</td>
<td>1314.636</td>
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<tr>
<td>AUC&lt;sub&gt;0-1&lt;/sub&gt; (ng.h/mL)</td>
<td>12199.474</td>
<td>11976.272</td>
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<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.h/mL)</td>
<td>12799.684</td>
<td>12448.656</td>
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The 90% confidence intervals for AUC and C<sub>max</sub> for test versus reference product for pioglitazone are within predefined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 15 mg, 30 mg and 45 mg strengths of the product meet the criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence study on the 45 mg strength can be extrapolated to the 15 mg and 30 mg strengths.

**Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for these applications.

**Efficacy**
No new efficacy data were submitted and none were required for these applications.

**Safety**
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with that for the originator products. The PIL is consistent with the SmPCs and in line with current guidelines. The labelling is in-line with current guidelines.
MAA Forms
The MAA forms are satisfactory.

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.

Pharmacovigilance System and Risk Management Plan
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.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of these products from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The quality characteristics of Pioglitazone Intas 15mg, 30mg and 45mg 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. The pharmacodynamic, pharmacokinetic and toxicological properties of pioglitazone are well-known.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Pioglitazone Intas 45mg tablets and its respective reference product Actos 45 mg Tablets (Takeda Global Research and Development Centre (Europe) Limited, UK). As the 15 mg, 30 mg and 45 mg strengths of the product meet the biowaiver criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence study on the 45 mg strength can be extrapolated to the 15 mg and 30mg strengths.

SAFETY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of pioglitazone is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.
PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products, and in line with current guidelines.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with pioglitazone is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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