Professional Information for

CIPLA-PIOGLITAZONE 15 / 30 (TABLETS)

SCHEDULING STATUS:

S3

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLA-PIOGLITAZONE 15 (Tablets)

CIPLA-PIOGLITAZONE 30 (Tablets)

COMPOSITION:

Each **CIPLA-PIOGLITAZONE 15** tablet for oral administration contains pioglitazone hydrochloride equivalent to 15 mg pioglitazone.

Each **CIPLA-PIOGLITAZONE 30** tablet for oral administration contains pioglitazone hydrochloride equivalent to 30 mg pioglitazone.

Inactive ingredients include carboxymethyl cellulose calcium, hydroxypropyl cellulose, lactose monohydrate, and magnesium stearate.

Contains lactose.

PHARMACOLOGICAL CLASSIFICATION:

A 21.2 Oral hypoglycaemics.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Pioglitazone is a thiazolidinedione antidiabetic agent that is effective only in the

presence of insulin. Its primary action is to decrease insulin resistance at peripheral sites and in the liver, resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output.

Pioglitazone is a selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues relevant for insulin action, such as adipose tissue, skeletal muscle and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the homeostasis of glucose and lipid metabolism.

Pharmacokinetic properties:

Absorption:

Pioglitazone is rapidly absorbed after oral administration, with peak concentrations observed within 2 hours. The bioavailability exceeds 80 %. Food slightly delays the time to peak serum concentrations, but does not alter the extent of absorption.

Distribution:

Pioglitazone is extensively protein bound (> 99 %) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (> 98 %) to serum albumin.

Biotransformation:

Pioglitazone is extensively metabolised by hydroxylation and oxidation to several active metabolites. Metabolites M-II and M-IV (hydroxyl derivatives of pioglitazone) and M-III (keto-derivative of pioglitazone) are pharmacologically active. The

cytochrome P450 plays an important role in the metabolism of pioglitazone. The major cytochrome P450 isoforms involved in the hepatic metabolism of pioglitazone are CYP2C8 and CYP3A4, with contributions from a variety of other isoforms, including the mainly extrahepatic CYP1A1. The metabolites are also partly converted to glucuronide or sulphate conjugates.

Excretion and elimination:

Approximately 15 % to 30 % of the pioglitazone dose is recovered in the urine, following oral administration. Renal elimination of pioglitazone is negligible, and the agent is excreted primarily as metabolites and their conjugates. Apparent clearance is 5 to 7 litres per hour. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the faeces.

INDICATIONS:

CIPLA-PIOGLITAZONE is indicated as an adjunctive therapy to diet and exercise in the management of patients with Type 2 diabetes (non-insulin dependent diabetes mellitus, NIDDM).

CIPLA-PIOGLITAZONE may be used as monotherapy or in combination with a sulphonylurea, metformin, or insulin when diet and exercise plus the single agent do not result in adequate glycaemic control.

CONTRAINDICATIONS:

CIPLA-PIOGLITAZONE is contraindicated in patients:

- With known hypersensitivity to pioglitazone or any of the components of the formulation.

- With impaired liver function or active liver disease or serum transaminase levels exceeding 2,5 times the upper limit of normal.
- In cardiac failure.
- Who are pregnant or lactating.
- With Type 1 diabetes mellitus.
- With diabetic ketoacidosis.
- Children: Safety and effectiveness of **CIPLA-PIOGLITAZONE** in paediatric patients have not been established.

WARNINGS AND SPECIAL PRECAUTIONS:

CIPLA-PIOGLITAZONE exerts its antihyperglycaemic effect only in the presence of insulin. Therefore, **CIPLA-PIOGLITAZONE** should not be used in patients with Type 1 diabetes or for the treatment of diabetic ketoacidosis (see **"CONTRAINDICATIONS"**).

Liver function:

The periodic monitoring of liver function is essential during treatment with **CIPLA-PIOGLITAZONE**, in view of thiazolidinedione class effects on the liver. Serum ALT (alanine transaminase) levels should be evaluated prior to the initiation of therapy with **CIPLA-PIOGLITAZONE** in all patients, every two months for the first year of therapy, and periodically thereafter.

Liver function tests should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, e.g. nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine. If ALT increases to 2,5 times baseline, treatment should be stopped. If jaundice is observed, **CIPLA-PIOGLITAZONE** therapy should be discontinued.

Therapy with **CIPLA-PIOGLITAZONE** should not be initiated if the patient exhibits clinical evidence of active liver disease, or if the ALT levels exceed 2,5 times the upper limit of normal (see **"CONTRAINDICATIONS"**). Patients with mildly elevated liver enzymes (ALT levels 1 to 2,5 times the upper limit of normal) at baseline, or any time during therapy with **CIPLA-PIOGLITAZONE**, should be evaluated to determine the cause of the enzyme elevation. Initiation of, or continuation of, therapy with **CIPLA-PIOGLITAZONE** in patients with mildly elevated liver enzymes should proceed with extreme caution and should include the appropriate clinical follow-up, which may include more frequent liver enzyme monitoring. If serum transaminase levels are increased (ALT > 2,5 times the upper limit of normal), or if the patient is jaundiced, **CIPLA-PIOGLITAZONE** therapy should be discontinued.

Ovulation:

In premenopausal anovulatory patients with insulin resistance, treatment with **CIPLA-PIOGLITAZONE** may result in resumption of ovulation. As a consequence of their improved insulin sensitivity, these patients may be at risk for pregnancy if adequate contraception is not used.

Hypoglycaemia:

Patients receiving **CIPLA-PIOGLITAZONE** in combination with insulin or oral hypoglycaemic agents may be at risk of hypoglycaemia and a reduction in the dose of the concomitant agent may be necessary. Either the **CIPLA-PIOGLITAZONE** dose or the insulin dose should be decreased if the patient reports hypoglycaemia or if plasma glucose concentrations decrease to less than 5,5 mmol/L (100 mg/dL) (see **"DOSAGE AND DIRECTIONS FOR USE"** and **"INTERACTIONS"**).

Bladder cancer:

Based on epidemiological data, treatment with pioglitazone, as in **CIPLA-PIOGLITAZONE**, for longer than 12 months may be associated with an increased risk of bladder cancer compared to no use of **CIPLA-PIOGLITAZONE** and this risk may increase with further duration of therapy.

CIPLA-PIOGLITAZONE should not be used in patients with bladder cancer or a history of bladder cancer. The risk of bladder cancer should be considered in the care of all patients treated with **CIPLA-PIOGLITAZONE**.

Bone fracture:

An increased incidence of bone fractures was seen in women treated with pioglitazone, as in **CIPLA-PIOGLITAZONE**, in a pooled analysis of clinical trials. No increase in fracture rates was observed in men. The risk of fractures should be considered in the long-term care of women treated with **CIPLA-PIOGLITAZONE**.

Haematological:

CIPLA-PIOGLITAZONE may cause a decrease in haemoglobin and haematocrit.

Oedema:

CIPLA-PIOGLITAZONE 30 should be used with caution in patients with oedema (see **"SIDE-EFFECTS"**). Since insulin and **CIPLA-PIOGLITAZONE** are both associated with fluid retention, concomitant administration may increase the risk of oedema (see **"INTERACTIONS"**).

Cardiac:

The use of **CIPLA-PIOGLITAZONE** is not recommended in patients with New York Heart Association Class III and IV cardiac status because pioglitazone causes plasma volume expansion. **CIPLA-PIOGLITAZONE** should be initiated at the lowest approved dose in patients with NYHA Class II systolic heart failure. If dose escalation is necessary, the dose should be increased gradually only after several months of treatment with careful monitoring for weight gain, oedema, or signs of congestive heart failure (CHF) exacerbation.

There have been postmarketing reports of cardiac failure when pioglitazone, as in **CIPLA-PIOGLITAZONE**, was used in combination with insulin or in patients with a history of cardiac failure (see **"INTERACTIONS"**). Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when **CIPLA-PIOGLITAZONE** is used in combination with insulin. **CIPLA-PIOGLITAZONE** should be discontinued if any deterioration in cardiac status occurs.

Weight gain:

There has been evidence of dose-related weight gain associated with the use of pioglitazone, 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 strictly adhere to a calorie-controlled diet.

Macular oedema:

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

Lactose:

CIPLA-PIOGLITAZONE contains lactose. Patients who are lactose intolerant and who take **CIPLA-PIOGLITAZONE** may experience unwanted side-effects, such as nausea, cramping, bloating, diarrhoea, and flatulence. **CIPLA-PIOGLITAZONE** should not be taken by patients with rare hereditary problems or a history of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Effects on the ability to drive and use machinery:

CIPLA-PIOGLITAZONE has no or negligible effect on the ability to drive and use machines. However, patients who experience visual disturbances should be cautious when driving or using machines.

INTERACTIONS:

Medicine interactions:

Combinations containing any of the following medications, depending on the amount

present, may result in interactions:

Oral contraceptives:

Administration of another thiazolidinedione with an oral contraceptive containing ethinyl oestradiol and norethindrone reduced the plasma concentrations of both hormones by approximately 30 %, which could result in loss of contraception.

Ketoconazole:

Concurrent use may decrease metabolism of **CIPLA-PIOGLITAZONE**.

Midazolam:

Concurrent administration may reduce midazolam serum concentrations.

Rifampicin:

Co-administration of **CIPLA-PIOGLITAZONE** and rifampicin is reported to result in a 54 % decrease in the AUC of pioglitazone. The dose of **CIPLA-PIOGLITAZONE** may need to be increased, based on clinical response, when rifampicin is concomitantly administered.

Gemfibrozil:

Co-administration of **CIPLA-PIOGLITAZONE** and gemfibrozil is reported to result in a 3-fold increase in the AUC of pioglitazone. Since there is a potential for dose-related adverse events with **CIPLA-PIOGLITAZONE**, a decrease in the dose of **CIPLA-PIOGLITAZONE** may be needed when gemfibrozil is concomitantly administered.

Insulin:

There have been postmarketing reports of cardiac failure when pioglitazone was used in combination with insulin. Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when **CIPLA-PIOGLITAZONE** is used in combination with insulin (see **"WARNINGS AND SPECIAL PRECAUTIONS"**). Since insulin and **CIPLA-PIOGLITAZONE** are both associated with fluid retention, concomitant administration may increase the risk of oedema. **CIPLA-PIOGLITAZONE** should be discontinued if any deterioration in cardiac status occurs.

Patients receiving **CIPLA-PIOGLITAZONE** in combination with insulin may be at risk of hypoglycaemia. Either the **CIPLA-PIOGLITAZONE** dose or the insulin dose should be decreased if the patient reports hypoglycaemia or if plasma glucose concentrations decrease to less than 5,5 mmol/L (100 mg/dL) (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"DOSAGE AND DIRECTIONS FOR USE"**).

Abiraterone:

Hypoglycaemia has been reported in patients with type 2 diabetes mellitus with concomitant use of **CIPLA-PIOGLITAZONE** and abiraterone, an inhibitor of the hepatic drug metabolising isoenzymes CYPD6 and CYP2C8. Frequent blood glucose monitoring should be done in these patients.

Laboratory abnormalities:

Haematological:

CIPLA-PIOGLITAZONE may cause decreases in haemoglobin and haematocrit. These changes may be related to increased plasma volume associated with **CIPLA-**

PIOGLITAZONE therapy and have not been associated with any significant haematologic clinical effects.

Serum transaminase levels:

Reversible elevations in ALT have been observed with **CIPLA-PIOGLITAZONE** (see **"SIDE-EFFECTS"**).

CPK levels:

Elevation of creatine phosphokinase levels (CPK) have been observed with **CIPLA-PIOGLITAZONE**.

PREGNANCY AND LACTATION:

The use of **CIPLA-PIOGLITAZONE** during pregnancy and lactation is contraindicated (see **"CONTRAINDICATIONS"**).

DOSAGE AND DIRECTIONS FOR USE:

Monotherapy:

Oral, initially 15 to 30 mg **CIPLA-PIOGLITAZONE** once daily without regard to meals. For patients who respond inadequately to the initial dose of **CIPLA-PIOGLITAZONE**, the dose can be increased in increments up to 45 mg once daily. For patients not responding adequately to monotherapy, combination therapy should be considered.

Note: Dose adjustment in patients with renal insufficiency is not recommended.

Combination therapy:

Sulphonylureas:

CIPLA-PIOGLITAZONE in combination with sulphonylureas may be initiated at 15 mg or 30 mg once daily. The current sulphonylurea dose can be continued upon initiation of **CIPLA-PIOGLITAZONE** therapy. If patients report hypoglycaemia, the dose of the sulphonylurea should be decreased.

Metformin:

CIPLA-PIOGLITAZONE in combination with metformin may be initiated at 15 mg or 30 mg once daily. The current metformin dose can be continued upon initiation of **CIPLA-PIOGLITAZONE** therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycaemia during combination therapy with **CIPLA-PIOGLITAZONE**.

Insulin:

CIPLA-PIOGLITAZONE in combination with insulin may be initiated at 15 mg or 30 mg once daily. The current insulin dose can be continued upon initiation of **CIPLA-PIOGLITAZONE** therapy. In patients receiving **CIPLA-PIOGLITAZONE** and insulin, either the **CIPLA-PIOGLITAZONE** dose or the insulin dose should be decreased if the patient reports hypoglycaemia or if plasma glucose concentrations decrease to less than 5,5 mmol/L (100 mg/dL). Further adjustments should be individualised based on glucose-lowering response (see **"INTERACTIONS"** and **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Maximum recommended dose:

The dose of **CIPLA-PIOGLITAZONE** should not exceed 45 mg once daily since doses higher than 45 mg once daily have not been studied in clinical studies.

SIDE-EFFECTS:

Adverse events reported with the use of **CIPLA-PIOGLITAZONE** included:

Infections and infestations:

Frequent:	Upper respiratory tract infection.
	Bronchitis (in combination with insulin).
Less frequent:	Sinusitis.

Neoplasms benign and malignant:

Less frequent:	Bladder cancer.

Blood and lymphatic system disorders:

Frequent:	Anaemia (in combination with metformin, and less frequently with monotherapy).

Metabolism and nutrition disorders:

Frequent:	Weight gain (in combination with metformin and/or sulphonylurea, or insulin; and with unknown frequency in monotherapy).
	Hypoglycaemia (in combination with metformin and a sulphonylurea, or insulin; and less frequently in combination with sulphonylurea only).

Less frequent:	Increased appetite (in combination with sulphonylurea).

Nervous system disorders:

Frequent:	Hypoaesthesia, headache.
	Dizziness (in combination with sulphonylurea).
Less frequent:	Insomnia.

Eye disorders:

Frequent:	Visual disturbances.
Frequency unknown:	Macular oedema.

Ear and labyrinth disorders:

Less frequent:	Vertigo (in combination with sulphonylurea).

Cardiac disorders:

Frequent:	Congestive heart failure and oedema.

Respiratory, thoracic and mediastinal disorders:

Frequent:	Pharyngitis.
	Dyspnoea (in combination with insulin).

Gastrointestinal disorders:

Frequent:	Flatulence (in combination with sulphonylurea; and less frequently in combination with metformin).

Hepatobiliary disorders:

Frequency unknown:	Hepatitis, raised hepatic enzymes.

Skin and subcutaneous tissue disorders:

Less frequent:	Sweating (in combination with sulphonylurea).

Musculoskeletal, connective tissue and bone disorders:

Frequent:	Bone fractures in women, myalgia. Arthralgia (in combination with metformin alone; or with metformin and sulphonylurea; or insulin). Back pain (in combination with insulin).

Renal and urinary disorders:

Frequent:	Haematuria (in combination with metformin).
Less frequent:	Glycosuria, proteinuria (in combination with sulphonylurea).

Reproductive system and breast disorders:

Frequent:	Erectile dysfunction (in combination with metformin).

General disorder:

Frequent:	Tooth disorders. Oedema (in combination with insulin).

Less frequent: Fatigue (in combination with sulphonylurea).

Investigations:

Frequent: Increased blood creatine phosphokinase (in combination with metformin and sulphonylurea).

Less frequent: Increased lactic dehydrogenase (in combination with sulphonylurea).

Frequency unknown: Increased alanine aminotransferase.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms (see **"SIDE-EFFECTS"**).

IDENTIFICATION:

CIPLA-PIOGLITAZONE 15: White, circular, flat bevelled edge, uncoated tablet with 'P15' debossed on one side and plain on the other side.

CIPLA-PIOGLITAZONE 30: White, circular, flat bevelled edge, uncoated tablet with 'P30' debossed on one side and plain on the other side.

PRESENTATION:

CIPLA-PIOGLITAZONE 15: Supplied in clear, colourless, transparent, PVC/PVDC and aluminium foil blister strips of 10 tablets, packed in

30.

CIPLA-PIOGLITAZONE 30: Supplied in clear, colourless, transparent, PVC/PVDC and aluminium foil blister strips of 10 tablets, packed in 30.

STORAGE INSTRUCTIONS:

Store at or below 25 ºC in blister packs. Protect from moisture and humidity. Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

CIPLA-PIOGLITAZONE 15: A40/21.2/0149

CIPLA-PIOGLITAZONE 30: A40/21.2/0150

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

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