PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg / 30 mg
PM02884001

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg (tablet)
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 30 mg (tablet)

COMPOSITION
Each tablet contains:
Pioglitazone hydrochloride equivalent to pioglitazone 15 or 30 mg.
Excipients: Lactose monohydrate, carboxymethyl cellulose calcium, hydroxypropyl cellulose and magnesium stearate.
Contains sugar (lactose).

PHARMACOLOGICAL CLASSIFICATION
A 21.2 Oral hypoglycaemics

PHARMACOLOGICAL ACTION
Pharmacodynamic properties
Pioglitazone hydrochloride (Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy] phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride) acts primarily by decreasing insulin resistance. Pharmacological studies indicate that it improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis.
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.

An additive effect on glycaemic control was observed when pioglitazone was used in combination with sulphonylureas, metformin or insulin.

Pharmacokinetic properties
Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady-state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30 % to 50 % of the peak total pioglitazone serum concentrations and 20 % to 25 % of the total area under the serum concentration-time curve (AUC). Maximum serum concentration (C_{max}), AUC and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone do not increase proportionally at doses of 15 mg and 30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg per day.

Absorption
Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption. The absolute bioavailability after oral intake of pioglitazone in humans is not known.

Distribution
The mean apparent volume of distribution (Vd/F) of pioglitazone following a single-oral dose of 7,5 mg is 0,63 ± 0,41 (mean ± SD) L/kg of body mass. 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.

Metabolism
Pioglitazone is extensively metabolized by hydroxylation and oxidation. The cytochrome P450 plays an important role in the metabolism of pioglitazone. The major cytochromes involved are CYP3A4 and CYP2C8. The metabolites also partly convert to glucuronide or sulphate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal agent-related species found in human serum following multiple dosing. At steady-state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30 % to 50 % of the total peak serum concentrations and 20 % to 25 % of the total AUC.
Pioglitazone incubated with expressed human P450 or human liver microsomes results in the formation of M-IV and to a much lesser degree, M-II. 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. Ketoconazole inhibited up to 85 % of hepatic pioglitazone metabolism *in vitro* at a concentration equal molar to pioglitazone. Pioglitazone did not inhibit P450 activity when incubated with human P450 liver microsomes. *In vitro* human studies have not been performed to investigate any induction of CYP3A4 by pioglitazone.

Excretion and Elimination
Following oral administration, approximately 15 % to 30 % of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the medicine is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the faeces.
The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance (CL/F) calculated to be 5 to 7 L/hr.

Special populations
Renal Insufficiency:
The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 60 mL/min) to severe (creatinine clearance < 30 mL/min) renal impairment when compared to normal subjects. No dose adjustment in patients with mild to moderate renal dysfunction is recommended.

Hepatic Insufficiency
Compared with normal controls, subjects with impaired hepatic function (Child-Pugh Grade B/C) have an approximate 45 % reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values.

Elderly
In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes were not of a magnitude that would be considered clinically relevant.

Gender
The mean C_{max} and AUC values were increased 20 % to 60 % in females. In controlled clinical trials, haemoglobin A1c (HbA1c) decreases from baseline were generally greater for females than for males. Since therapy should be individualised for each patient to achieve glycaemic control, no dose adjustment is recommended based on gender alone.

INDICATIONS
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes (non insulin dependent diabetes mellitus, NIDDM), as monotherapy or in combination with a sulphonylurea, metformin, or insulin when diet and exercise plus the single medicine does not result in adequate glycaemic control.

CONTRA-INDICATIONS
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS is contraindicated in patients with:
- known hypersensitivity to pioglitazone or any of the components of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS,
- impaired liver function with serum transaminase levels exceeding 2,5 times the upper limit of normal or active liver disease,
- cardiac failure or history of cardiac failure,
- pregnancy and lactation,
- type 1 diabetes mellitus or diabetic ketoacidosis,
- current bladder cancer or history of bladder cancer,
- uninvestigated macroscopic haematuria.

Children: Safety and effectiveness of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS in paediatric patients have not been established.

WARNINGS AND SPECIAL PRECAUTIONS
Liver function monitoring is essential.
Serum ALT (alanine transaminase) levels should be evaluated prior to the initiation of therapy with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS in all patients, every two months for the first year of therapy, and periodically thereafter.

In all clinical trials, a reduction in HbA_{1c} was accompanied by a significant mean increased body mass in PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS treated patients in a dose related manner.

Hypoglycaemia: patients receiving PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS in combination with insulin or oral hypoglycaemic medicines may be at risk of hypoglycaemia and a reduction in the dose of the concomitant medicine may be necessary.

Ovulation: In premenopausal anovulatory patients with insulin resistance, treatment with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 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.

Fluid retention and cardiac failure: PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS can cause significant plasma volume expansion and pre-load induced cardiac hypertrophy. PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS, can cause fluid retention when used alone or in combination with other antidiabetic medicines including insulin. Fluid retention may lead to or exacerbate 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), medical practitioners 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 HYDROCHLORIDE TABLETS MACLEODS 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 HYDROCHLORIDE TABLETS MACLEODS is used in combination with insulin. Since insulin and PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS are both associated with fluid retention, concomitant administration may increase the risk of oedema. Post marketing cases of peripheral oedema and cardiac failure have also been reported in patients with concomitant use of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS and nonsteroidal anti-inflammatory medicines, including selective COX-2 inhibitors.
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS should be discontinued if any deterioration in cardiac status occurs.

Elderly
Combination use with insulin should be considered with caution in the elderly because of increased risk of serious heart failure.
Due to 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 frequently with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS. Epidemiological studies have also suggested a small increased risk of bladder cancer in diabetic patients treated with pioglitazone, as in PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS.
Risk factors for bladder cancer should be assessed before initiating PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS treatment (risks include age, smoking history, exposure to some occupational or chemotherapy medicines e.g. cyclophosphamide or prior radiation treatment in the pelvic region).
Any macroscopic haematuria should be investigated before starting PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS therapy.
Patients should be advised to promptly seek the attention of their medical practitioner if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

Hepatic effect: In view of thiazolidinediones class effects on the liver, it is essential that patients treated with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS undergo periodic monitoring of liver enzymes. Liver function test should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine. If ALT increases to 2,5 times baseline, treatment should be stopped. If jaundice is observed, PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS therapy should be discontinued.
Therapy with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceeds 2,5 times the upper limit of normal. Patients with mildly elevated liver enzymes (ALT levels at 1 to 2,5 times the upper limit of normal) at baseline or any time during therapy with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS in patients with mildly elevated liver enzymes should proceed with extreme caution and 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, PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS therapy should be discontinued.

Haematologic: PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS may cause decreases in haemoglobin and haematocrit. Mean haemoglobin values declined by 2 % to 4 % in pioglitazone treated patients. These changes primarily occurs within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume and may not be associated with any significant haematologic clinical effects.

Weight gain: Dose related weight gain was seen with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS alone and in combination with other hypoglycaemic medicines. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Macular oedema: New onset or worsening (diabetic) macular oedema with decreased visual acuity have been reported with the use of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS. Medical practitioners should consider the possibility of macular oedema if a patient reports decreased visual acuity.

Others
An increased incidence in bone fractures in women has been reported in patients on treatment for up to 3,5 years.
Some epidemiological studies have suggested a similarly increased risk of fracture in both men and women.
The risk of fractures should be considered in the long term care of patients treated with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS.

It is important to instruct patients to adhere to dietary instructions and to have blood glucose and glycosylated haemoglobin tested regularly. During periods of stress such as fever, trauma, infection or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.

Laboratory tests
Liver enzyme monitoring is essential prior to initiation of therapy with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS in all patients and periodically thereafter. Patients who experience an unusually rapid increase in weight or oedema or who develop shortness of breath or other symptoms of heart failure while on PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS should immediately report these symptoms to their medical practitioner.
Patient should be told that blood test for liver function will be performed prior to the start of therapy, every two months for first year, and periodically thereafter. Patients should be told to seek immediate medical advice for unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

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

Lactose warning:
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS.
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS
Medicines Interactions
Oral Contraceptives:
Administration of another thiazolidinediones with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentration of both hormones by approximately 30 %, which could result in loss of contraception. The pharmacokinetics of co-administration of pioglitazone and oral contraceptives have not been evaluated in patients taking pioglitazone and an oral contraceptive. Therefore, additional caution regarding contraception should be exercised in patients receiving PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS and an oral contraceptive.

Glipizide: In healthy volunteers, co-administration of pioglitazone (45 mg once daily) and glipizide (5 mg once daily) for seven days did not alter the steady-state pharmacokinetics of glipizide.

Digoxin: In healthy volunteers, co-administration of pioglitazone (45 mg once daily) with digoxin (0,25 mg once daily) for seven days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: In healthy volunteers, co-administration of pioglitazone (45 mg once daily) for seven days with warfarin did not alter the steady-state pharmacokinetics of warfarin. In addition pioglitazone has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Metformin: In healthy volunteers, co-administration of metformin (1000 mg) and pioglitazone (45 mg) after seven days of pioglitazone (45 mg once daily) did not alter the pharmacokinetics of the single dose of metformin.

Cytochrome P450 isoform CYP3A4 is partially responsible for the metabolism of pioglitazone. Specific formal pharmacokinetic interaction studies have not been conducted with pioglitazone and other medicines metabolised by this enzyme, such as: erythromycin, calcium channel blockers, cisapride, corticosteroids, ciclosporin, HMG-CoA reductase inhibitors, tacrolimus, triazolam, and trimetrexate, as well as inhibitory medicines such as ketoconazole and itraconazole. *In vitro*, ketoconazole appears to significantly inhibit the metabolism of pioglitazone. Patients receiving ketoconazole concomitantly with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS should be evaluated more frequently with respect to glycaemic control.

An inhibitor of CYP2C8 (such as gemfibrozil) may increase the AUC of pioglitazone and an inducer of CYP2C8 (such as rifampicin) may decrease the AUC of pioglitazone.

Co-administration of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS with rifampicin is reported to result in a 54 % decrease in AUC of pioglitazone. The PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS dose may need to be increased based on clinical response when rifampicin is concomitantly administered.

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

PREGNANCY AND LACTATION
Safety and effectiveness of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS in pregnancy and lactation have not been established (see Contraindications).

DOSAGE AND DIRECTIONS FOR USE
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS should be taken once daily without regard to meals.
The management of antidiabetic therapy should be individualised.

Monotherapy
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS monotherapy in patients not adequately controlled with diet and exercise may be initiated at 15 mg or 30 mg once daily. For patients who respond inadequately to the initial dose of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS, 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.

Combination therapy
Sulphonylureas: PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS in combination with a sulfonylurea may be initiated at 15 mg or 30 mg once daily. The current sulfonylurea dose can be continued upon initiation of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS therapy. If patients report hypoglycaemia, the dose of the sulfonylurea should be decreased.

Metformin
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 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 PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycaemia during combination therapy with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS.

Insulin
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 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 PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS therapy. In patients receiving PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS and insulin, either the PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS dose or the insulin dose should be decreased if patient reports hypoglycaemia or if plasma glucose concentration decreases to less than 5,5 mmol/l (100 mg/dl). Further adjustments should be individualised based on glucose-lowering response.

Maximum Recommended Dose
The dose of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS should not exceed 45 mg once daily since doses higher than 45 mg once daily have not been studied. No studies of more than 30 mg once daily have been conducted in combination therapy.
Dose adjustment in patients with renal insufficiency is not recommended
Therapy with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2,5 times the upper limit of normal) at start of therapy. Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS and periodically thereafter.
No data are available on the use of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS in combination with another thiazolidinediones.

SIDE EFFECTS
Clinical adverse event reported when PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS was used in combination with sulphonylureas, metformin, or insulin were generally similar to those reported during PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS monotherapy with the exception of an increase in the occurrence of mild to moderate oedema in the insulin combination study. Mild to moderate hypoglycaemia was reported during combination therapy with sulphonylureas or insulin.

In post marketing experience with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS, congestive heart failure has been reported in patients both with and without pre-existing cardiac disease. In post-marketing experience with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these have involved hepatic failure with and without fatal outcome, although causality has not been established.

System organ class/ Adverse event	Frequency of side effects by treatment regimen				
	Monotherapy	Combination therapy with			
		metformin	sulphonylurea	metformin and sulphonylurea	insulin
Infections and infestations					
upper respiratory tract infection	frequent	frequent	frequent	frequent	frequent
bronchitis					frequent
sinusitis	less frequent	less frequent	less frequent	less frequent	less frequent
Neoplasms benign, malignant and unspecified (including cysts and polyps)					
bladder cancer	less frequent	less frequent	less frequent	less frequent	less frequent
Blood and lymphatic system disorders					
anaemia		frequent			
Immune system disorders					
hypersensitivity and allergic reactions	frequency not known	frequency not known	frequency not known	frequency not known	frequency not known
Metabolism and nutrition disorders					
hypoglycaemia			less frequent	frequent	frequent
increased appetite			less frequent		
Nervous system disorders					
hypoaesthesia	frequent	frequent	frequent	frequent	frequent
headache		frequent	less frequent		
dizziness			frequent		
insomnia	less frequent	less frequent	less frequent	less frequent	less frequent
Eye disorders					
visual disturbance	frequent	frequent	less frequent		
macular oedema	frequency not known	frequency not known	frequency not known	frequency not known	frequency not known
Ear and labyrinth disorders					
vertigo			less frequent		
Cardiac disorders					
heart failure					frequent
Respiratory, thoracic, mediastinal disorders					
dyspnoea					frequent
Gastrointestinal disorders					
flatulence		less frequent	frequent		
Skin and subcutaneous tissue disorders					
sweating			less frequent		
Musculoskeletal and connective tissue disorders					
bone fracture	frequent	frequent	frequent	frequent	frequent
arthralgia		frequent		frequent	frequent
back pain					frequent
Renal and urinary disorders					
haematuria		frequent			
glycosuria			less frequent		
proteinuria			less frequent		
Reproductive system and breast disorders					
erectile dysfunction		frequent			
General disorders and administration site conditions					
oedema					
fatigue			less frequent		
Investigations					
weight gain	frequent	frequent	frequent	frequent	frequent
increased blood creatine phosphokinase				frequent	
increased lactic dehydrogenase			less frequent		
increased alanine amino transferase	frequency not known	frequency not known	frequency not known	frequency not known	frequency not known

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

IDENTIFICATION
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg
White, circular, flat face, bevelled edge, uncoated tablet debossed with 'ML 86' on one side and plain on the other side.

PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 30 mg
White, circular, flat face, bevelled edge, uncoated tablet debossed with 'ML 87' on one side and plain on the other side.

PRESENTATION
Cold form Alu/Alu blister pack consisting of aluminium foil laminated to oriented polyamide on one side and laminated to PVC on the other side as the forming material and plain aluminium foil as the lidding material. Each blister contains 10 tablets and 3 such blisters are packed in a carton along with pack insert.
Bulk pack consisting of white plastic container (HDPE), which is sealed at the mouth with an aluminium tagger and is closed with a white HDPE screw–on lid. Pack size include 30 tablets or 90 tablets.

STORAGE INSTRUCTIONS
Store at or below 30 °C in the original container. Protect from moisture and humidity. The blisters must be kept in the carton until required for use. Keep the HDPE container closed.
KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER
PIOGLTAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg: 46/21.2/0257
PIOGLTAZONE HYDROCHLORIDE TABLETS MACLEODS 30 mg: 46/21.2/0258

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
Macleods Pharmaceuticals SA (Pty) Ltd.
Office Block 1, Bassonia Estate Office Park (East)
1 Cussonia Drive, Bassonia Rock, Ext. 12, Alberton,
South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT
20 March 2018

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S3

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg (tablet)
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 30 mg (tablet)

Read all of this leaflet carefully before you start taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

WHAT PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS CONTAIN?
Each tablet contains:
Pioglitazone hydrochloride equivalent to pioglitazone 15 or 30 mg
Other Ingredients: Lactose monohydrate, carboxymethyl cellulose calcium, hydroxypropyl cellulose and magnesium stearate.
Contains sugar (lactose).

WHAT PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS ARE USED FOR?
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS is used to treat adult patients with type 2 diabetes (also called 'non-insulin dependent diabetes') in conjunction with a diet and exercise programme to control your blood glucose levels. PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS can be taken on its own or together with other medicines to treat diabetes (medicines taken by mouth or insulin) when diet and exercise plus the single medicine did not control your blood sugar levels adequately.

BEFORE YOU TAKE PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS
Do not take PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS:
- If you are allergic to pioglitazone hydrochloride or any of the ingredients of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS.
- If you have kidney or liver problems.
- If you are treated for heart failure or recently had a heart attack or have severe problems with your circulation (such as shock) or have breathing difficulties.
- If you have uncontrolled diabetes, with severe hyperglycaemia (high blood glucose), nausea, vomiting, dehydration, rapid weight loss or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or unusual fruity odour of the breath.
- If you have or have ever had bladder cancer.
- If you have blood in your urine that your doctor has not checked.
- If you are pregnant or breastfeeding.

PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS should not be given to children.

Take special care with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS
Tell your doctor:
- about any past or present medical problems
- about any risk factors for heart disease
- if you have a family history of heart disease
- about any allergies you have or have had
- if you have kidney or liver disease.

While taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS:
- Continue your exercise and diet program and test your blood sugar regularly while taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS. Your doctor will monitor your diabetes and may perform blood tests on you from time to time to make sure your kidneys and your liver are functioning normally.
- Monitor your blood glucose levels regularly if you are taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS with other anti-diabetic medicine such as a sulphonylurea or insulin. If you take PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS with other medicines for diabetes, it is more likely that your blood sugar could fall below the normal level (hypoglycaemia). Your doctor may reduce the dose of the other medicine.
- If you are a woman who does not normally ovulate, e.g. If you have 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 HYDROCHLORIDE TABLETS MACLEODS. If this applies to you, use appropriate contraception to avoid the possibility of an unplanned pregnancy.
- Some patients with long-standing type 2 diabetes mellitus and the elderly can develop heart failure while taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS. 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).
- Taking anti-inflammatory medicines with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS may lead to heart failure and fluid retention or swelling. Inform your doctor immediately if you experience symptoms of fluid retention and swelling.
- Bladder cancer has been experienced less frequently in patients taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS. Signs and symptoms include blood in your urine, pain when urinating or a sudden need to urinate. If you experience any of these, inform your doctor as soon as possible.
- Inform your doctor if you experience symptoms of nausea, vomiting, stomach pain, tiredness, loss of appetite, dark urine or yellowing of the skin (jaundice). Your doctor will test your liver and may stop treatment with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS.
- You may experience a reduction in blood count (anaemia) – with symptoms of tiredness, headaches, being short of breath when exercising, rapid heart beat, difficulty concentrating, dizziness, leg cramps, difficulty falling asleep and looking pale.
- PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS may cause you to gain weight.
- PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS may cause blurred vision due to swelling (or fluid) at the back of the eye. If you experience this symptom for the first time, talk to your doctor as soon as possible. If you already have blurred vision and the symptom gets worse, inform your doctor as soon as possible.
- PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS may cause bone fractures in both men and women. Inform your doctor immediately if you fracture any of your bones.

Taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS with food and drink:
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS can be taken with or without food.

Pregnancy and breastfeeding

> If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS.

PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS should not be taken during pregnancy
Tell your doctor or pharmacist if you are breastfeeding or plan to breastfeed. PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS should not be taken while you are breastfeeding.

Driving and using machinery
If you experience symptoms of hypoglycaemia (low blood sugar levels with symptoms of weakness, dizziness, increased sweating, fast heartbeat, vision disorders or difficulty in concentration) while taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS, you should refrain from driving or operating machinery

Important information about some of the ingredients of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS:
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS contains lactose. Patients with the rare hereditary conditions of lactose/fructose or galactose intolerance should not take PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS.

Taking other medicines with PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS

> Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines).

Only take other medicines while you are on PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS if your doctor tells you that you can. Tell your doctor if you take any of the following medicines:
- gemfibrozil (used to lower cholesterol)
- rifampicin (used to treat tuberculosis and other infections)
- oral contraceptive medicines (additional contraceptive measures may be required while taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS as well)
- other medicines used to treat diabetes
- anti-inflammatory medicines and PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS at the same time. You may need more frequent blood glucose tests or your doctor may adjust the dosage of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS.

HOW TO TAKE PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS

> Do not share medicines prescribed for you with any other person.
> Always take PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. If you have the impression that the effect of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS is too strong or too weak talk to your doctor or pharmacist.

Your doctor will tell you how many PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS to take and how long you should continue to take them.
Take PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS with or after a meal.
Do not crush or chew the tablets. Swallow each tablet with a glass of water.
The usual starting dose is one tablet of 15 mg or of 30 mg of PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS to be taken once daily. Your doctor may increase the dose to a maximum of 45 mg once a day.

If you forget to take PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS
It is important to take your PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS regularly at the same time each day. If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. In that case, just carry on with the next dose as normal. Do not take a double dose to make up for a forgotten dose.

If you stop taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS
Do not stop taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS just because you feel better. It is important that you carry on taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS for as long as your doctor tells you.

If you take more PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS than you should

> In the event of overdosage consult your doctor or pharmacist. If neither is available contact the nearest hospital or poison control centre.

POSSIBLE SIDE EFFECTS
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS can have side effects.
Not all the side effects reported for PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS, please consult your doctor, pharmacist or healthcare professional for advice.
If any of the following happen to you, stop taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS and tell your doctor immediately or go to the casualty department at your nearest hospital:
- Sudden signs of allergy – including skin rash, itching or hives; swelling of the face, lips or tongue, shortness of breath or difficulty breathing
- 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).
- Bladder cancer. Signs and symptoms include blood in your urine, pain when urinating or a sudden need to urinate. If you experience any of these symptoms inform your doctor as soon as possible.

These are all very serious side effects which occur less frequently. You may need urgent medical attention or hospitalisation.

If any of the following happen, tell your doctor immediately or go to casualty at your nearest hospital:
- Hypoglycaemia - low sugar (glucose) levels in the blood, especially if you are taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS with other anti-diabetic medicines such as a sulphonylurea or insulin. Symptoms may include sweating, weakness, hunger, dizziness, trembling, headache, flushing or paleness, numbness, having a fast, pounding heartbeat.
- Blurred vision due to swelling (or fluid) at the back of the eye.
- Abnormalities in liver function tests or hepatitis (inflammation of the liver; this may cause tiredness, loss of appetite, weight loss, with or without yellowing of the skin or whites of the eyes). If this happens to you, stop taking PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS and inform your doctor.
- Broken or fractured bones.

Tell your doctor if you notice any of the following
Frequent side effects:
- respiratory infection
- numbness
- headache
- dizziness
- abnormal vision
- shortness of breath
- reduction in red blood cell count (anaemia)
- flatulence
- joint pain
- back pain
- blood in the urine
- impotence
- swelling of the arms and legs (oedema)
- weight gain

Less frequent side effects:
- inflammation of the sinuses (sinusitis)
- increased appetite
- difficulty sleeping (insomnia)
- spinning sensation (vertigo)
- sweating
- tiredness
- laboratory tests may show: sugar in the urine, proteins in the urine, increase in enzymes.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

STORING AND DISPOSING OF PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS
Store at or below 30 °C (room temperature) in the original container.
Protect from moisture and humidity. The blisters must be kept in the carton until required for use.
Keep the HDPE container closed.
KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

> Return all unused medicine to your pharmacist.
> Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

PRESENTATION:
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg and 30 mg
Cold form Alu/Alu blister pack consisting of aluminium foil laminated to oriented polyamide on one side and laminated to PVC on the other side as the forming material and plain aluminium foil as the lidding material. Each blister contains 10 tablets and 3 such blisters are packed in a carton along with pack insert.
Bulk pack consisting of white plastic container (HDPE), which is sealed at the mouth with an aluminium tagger and is closed with a white HDPE screw–on lid. Pack size include 30 tablets or 90 tablets.

IDENTIFICATION
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg
White, circular, flat face, bevelled edge, uncoated tablet debossed with 'ML 86' on one side and plain on the other side
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 30 mg
White, circular, flat face, bevelled edge, uncoated tablet debossed with 'ML 87' on one side and plain on the other side.

REGISTRATION NUMBER/REFERENCE NUMBER
PIOGLTAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg: 46/21.2/0257
PIOGLTAZONE HYDROCHLORIDE TABLETS MACLEODS 30 mg: 46/21.2/0258

NAME AND ADDRESS OF REGISTRATION HOLDER
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EIENDOMSNAAM EN DOSEERVORM
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg (tablet)
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 30 mg (tablet)

SAMESTELLING
Elke tablet bevat:
Pioglitasoonhidrochloried ekwivalent aan pioglitasoon 15 of 30 mg.
Ekspiënte: Laktosemonohidraat, karboksimetielsellulose, hidroksipropielsellulose en magnesiumstearaat.
Bevat suiker (laktose).

FARMAKOLOGIESE KLASSIFIKASIE
A 21.2 Hipoglukemiesemiddels

FARMAKOLOGIESE WERKING
Farmakodinamiese eienskappe
Pioglitasoonhidrochloried (Pioglitasoon [(±)-5-[[4-[2-(5-etiel-2-piridinil)etoksi]fenielmetiel]-2,4-] tiasolidinedioon monohidrochloried) werk hoofsaaklik deur insulienweerstand te verminder. Farmakologiese studies toon aan dat dit die sensitiwiteit teen insulien in die spier- en vetweefsel verbeter en glukoneogenese in die lewer inhibeer.

Pioglitasoon is 'n selektiewe agonis vir peroksisoom proliferasiegeaktiveerde reseptor gamma (PPARγ). PPAR-reseptore word in weefsels waarin insulienwerking belangrik is gevind, soos vetweefsel, skeletspier en die lewer. Die aktivering van PPARγ kernreseptore moduleer die transkripsie van 'n aantal responsiewe gene betrokke by die homeostase van glukose- en lipiedmetabolisme.

'n Additiewe effek op glukemiebeheer is waargeneem wanneer pioglitasoon in kombinasie met sulfonielureum, metformien of insulien gebruik is.

Farmakokinetiese eienskappe
Totale serumvlakke van pioglitasoon (pioglitasoon plus sy aktiewe metaboliete) bly vir 24 hoog na een keer daaglikse dosering. Plato serumkonsentrasies van beide pioglitasoon en totale pioglitasoon word binne 7 dae bereik. Teen platokonsentrasie bereik twee van die farmakologies aktiewe metaboliete, Metaboliete III (M-III) en IV (M-IV) groter of gelyke konsentrasies as pioglitasoon. In beide gesonde vrywilligers en pasiënte met tipe 2 diabetes bestaan ongeveer 30 % tot 50 % van die piek pioglitasoon serumkonsentrasies uit pioglitasoon en bestaan 20 % tot 30 % van die totale area onder die serumkonsentrasie-tydkurwe (AOK).

Maksimum serumkonsentrasie (K_{maks}), AOK en trogserumkonsentrasies (K_{min}) vir beide pioglitasoon en totale pioglitasoon neem nie proporsioneel toe teen dosisse van 15 mg en 30 mg per dag nie. Daar bestaan 'n effens kleiner as proporsionele toename vir pioglitasoon en totale pioglitasoon teen dosisse van 60 mg per dag.

Absorpsie
Na orale toediening in die vastende toestand word pioglitasoon eers na 30 minute in die serum meetbaar, met piekkonsentrasies wat binne twee ure voorkom. Voedsel vertraag die tyd tot piek serumkonsentrasie effens na 3 tot 4 ure, maar verander nie die mate van absorpsie nie. Die absolute biobeskikbaarheid na die orale inname van pioglitasoon in mense is nie bekend nie.

Verspreiding
Die gemiddelde oënskynlike volume van verspreiding (Vd/F) van pioglitasoon na 'n enkel orale dosis van 7,5 mg is 0,63 ± 0,41 (gem. ± SA) L/kg liggaamsmassa. Pioglitasoon is sterk proteïengebonde (> 99 %) in menslike serum, hoofsaaklik aan serumalbumien. Pioglitasoon bind ook aan ander serumproteïene, maar met les affiniteit. Die metaboliete M-III en M-IV word ook sterk (> 98 %) aan serumalbumien gebind.

Metabolisme
Pioglitasoon word uitgebreid deur hidroksilering en oksidasie gemetaboliseer. Die sitochroom P450 speel 'n belangrike rol in die metabolisme van pioglitasoon. Die belangrikste sitochrome betrokke is CYP3A4 en CYP2C8. Die metaboliete word ook gedeeltelik na glukuronied- of sulfaatkonjugate omgeskakel. Metaboliete M-II en M-IV (hidroksiderivate van pioglitasoon) en M-III (keto-derivaat van pioglitasoon) is farmakologies aktief in dieremodelle van tipe 2 diabetes. Behalwe pioglitasoon, is M-III en M-IV die belangrikste middelverwante spesies wat na veelvuldige dosering in menslike serum gevind word. Teen platokonsentrasie, in beide gesonde vrywilligers en in pasiënte met tipe 2 diabetes, beset pioglitasoon ongeveer 30 % tot 50 % van die totale piek serumkonsentrasie en 20 % tot 25 % van die totale AOK.
Pioglitasoon, geïnkubeer uit menslike P450 of menslike lewermikrosome lei tot die vorming van M-IV en tot 'n baie kleiner mate, M-II. Die belangrike sitochroom P450 isovorms in die lewermetabolisme van pioglitasoon is CYP2C8 en CYP3A4, met bydraes van 'n verskeidenheid ander isovorms, insluitende die hoofsaaklik ekstrahepatiese CYP1A1. *In vitro* het ketokonasool tot soveel as 85 % van die lewermetabolisme van pioglitasoon teen 'n konsentrasie gelykmolaar aan pioglitasoon geïnhibeer. Pioglitasoon het nie P450-aktiwiteit geïnhibeer wanneer dit met menslike P450 lewermikrosoom geïnkubeer is nie. *In vitro* menslike studies om die induksie van CYP3A4 deur pioglitasoon te ondersoek, is nie uitgevoer nie.

Uitskeiding en eliminasie
Na orale toediening word ongeveer 15 % tot 30 % van die pioglitasoondosis in die urien herwin. Nierelimnasie van pioglitasoon is minimaal en die medisyne word hoofsaaklik as metaboliete en hul konjugate uitgeskei. Daar word vermoed dat die meeste van die orale dosis onveranderd, of as metaboliete in die gal uitgeskei en in die feses geëlimineer word.

Die gemiddelde serumhalfleeftyd van pioglitasoon en totale pioglitasoon wissel van 3 tot 7 ure en 16 tot 24 ure, respektiewelik. Pioglitasoon het 'n oënskynlike opruiming (CL/F) wat op 5 tot 7 L/uur bereken word.

Spesiale populasies
Onderwerkende nierfunksie:
Die serum eliminasiehalfleeftyd van pioglitasoon, M-III en M-IV bly onverander in pasiënte met matige (kreatinienopruiming van 30 tot 60 mL/min) tot erg (kreatinienopruiming < 30 mL/min) ingekorte nierfunksie in vergelyking met normale individue. Geen dosisaanpassing word in pasiënte met geringe tot matig ingekorte nierfunksie aanbeveel nie.

Onderwerkende lewerfunksie:
In vergelyking met normale kontroles, toon individue met onderwerkende lewerfunksie (Child-Pugh graad B/C) 'n ongeveer 45 % afname in gemiddelde piekkonsentrasies van pioglitasoon en totale pioglitasoon, maar geen verandering in die gemiddelde AOK nie.

Bejaardes:
In gesonde bejaarde individue is die gemiddelde piek serumkonsentrasies van pioglitasoon en totale pioglitasoon nie beduidend anders nie. Die AOK-waardes is egter effens hoër en die terminale halfleeftydwaardes effens langer as in jonger individue. Die aard van hierdie veranderinge word nie as klinies betekenisvol beskou nie.

Geslag:
Die gemiddelde K_{maks}- en AOK-waardes was 20 % tot 60 % hoër in vroue. In gekontroleerde kliniese proewe was hemoglobien A1c (HbA1c) afnames vanaf basislyn groter vir vroue as vir mans. Aangesien terapie vir elke pasiënt geïndividualiseer behoort te word om glukemiebeheer te kry, word geen dosisaanpassing volgens geslag alleen aanbeveel nie.

INDIKASIES
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS word aangedui as byvoeging tot dieet en oefening om glukemiebeheer in pasiënte met tipe 2 diabetes (nie-insulienafhanklike diabetes mellitus (NIADM), as monoterapie of in kombinasie met 'n sulfonielureum, metformien, of insulien wanneer dieet en oefening plus die enkel medisyne nie tot volkome glukemiebeheer lei nie.

KONTRA-INDIKASIES
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS word teenaangedui in pasiënte met:
- Bekende hipersensitiwiteit teen pioglitasoon of enige van die komponente van **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS**.
- Ingekorte lewerfunksie met serumtransaminasevlakke wat 2,5 keer die boonste limiet van normale of aktiewe lewersiekte oorskry.
- Hartversaking of 'n geskiedenis van hartversaking.
- Swangerskap en laktasie
- Tipe 1 diabetes mellitus of diabetiese keto-asidose.
- Huidige blaaskanker of geskiedenis daarvan.
- Nie-ondersoekte makroskopiese hematurie.

Kinders: Die veiligheid en effektiwiteit van **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** in pediatriese pasiënte is nie vasgestel nie.

WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS
Die monitering van lewerfunksie is noodsaaklik.
Serum ALT(alanientransaminase) behoort vóór die begin van terapie met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** in alle pasiënte geëvalueer te word, elke twee maande vir die eerste jaar van terapie, en dan periodiek daarna.

In alle kliniese proewe het 'n afname in HbA_{1c} met 'n beduidende gemiddelde toename in liggaamsmassa in pasiënte wat met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** behandel is, op 'n dosisverwante manier gepaard gegaan.

Hipoglukemie:
Pasiënte wat **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** in kombinasie met insulien of orale hipoglukemiemiddels ontvang, mag 'n risiko van hipoglukemie loop en 'n afname in die dosis van die meegaande medisyne mag nodig wees.

Ovulasie:
In pre-menopousale, anovulatoriese pasiënte met insulienweerstand, mag die behandeling met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** tot 'n hervatting van ovulasie lei. Hierdie pasiënte mag die risiko van swangerskap loop as voldoende geboortebeperking nie toegepas word nie.

Vloeistofretensie en hartversaking:
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS kan beduidende plasmavolumevergroting en voorladinggeïnduseerde hipertrofie van die hart veroorsaak. **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** kan vloeistofretensie veroorsaak wanneer dit alleen of in kombinasie met ander antidiabetiese medisyne, insluitende insulien gebruik word. Vloeistofretensie kan tot hartversaking lei of dit vererger.
Wanneer pasiënte wat ten minste een risikofaktor vir die ontwikkeling van hartversaking het (bv. vorige miokardiese infarksie of simptomatiese koronêre slagaarsiekte, of bejaardes), behoort mediese praktisyns met die laagste beskikbare dosis te begin en die dosis daarna geleidelik te verhoog. Pasiënte behoort onder observasie gehou te word vir tekens en simptome van hartversaking, massatoename of edeem, veral diegene met beperkte hartreserwe. Nabemarkingsgevalle van hartversaking is aangemeld nadat **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** in kombinasie met insulien gebruik is, asook in pasiënte met 'n geskiedenis van hartversaking. Pasiënte behoort vir tekens en simptome van hartversaking, massatoename en edeem geobserveer te word wanneer **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** in kombinasie met insulien gebruik word. Aangesien insulien en **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** beide met vloeistofretensie geassosieer word, mag die meegaande toediening die risiko van edeem verhoog. Nabemarkingsgevalle van perifere edeem en hartversaking is ook in pasiënte aangemeld met die meegaande gebruik van **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** en nie-steroïed anti-inflammatoriese middels, insluitende selektiewe COX-2 inhibeerders, aangemeld. **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** behoort gestaak te word as enige agteruitgang van die hartstatus voorkom.

Bejaardes:
Die kombinasiegebruik saam met insulien behoort met sorg oorweeg te word weens die toenemende risiko van ernstige hartversaking.
Weens ouderdomsverwante risiko's (veral blaaskanker, frakture en hartversaking), behoort die balans van voordele teenoor die risiko's in bejaardes versigtig teen mekaar opgeweeg te word, beide vóór en gedurende behandeling.

Blaaskanker
Gevalle van blaaskanker is dikwels met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** aangemeld. Uit epidemiologiese studies het dit geblyk dat daar ook 'n klein toename in die risiko van blaaskanker in diabetiese pasiënte is wat met pioglitasoon, soos in **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS**, behandel is.
Risikofaktore vir blaaskanker behoort geëvalueer te word voordat behandeling met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** oorweeg word (risiko's sluit die volgende in: ouderdom, rookgeskiedenis, blootstelling aan sekere beroeps- of chemoterapeutiese medisyne bv. siklofosfamied of vorige bestralingsbehandeling in die bekkenarea).
Enige makroskopiese hematurie behoort ondersoek te word voordat met terapie met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** begin word.
Pasiënte behoort aangeraai te word om so gou as moontlik hul dokter te raadpleeg wanneer makroskopiese hematurie of ander simptome soos disurie of urienaandrang gedurende behandeling ontwikkel.

Lewereffek:
In die lig van tiasolidinedioonklas effekte op die lewer is dit noodsaaklik dat pasiënte wat met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** behandel word, periodieke monitering van lewerensieme ondergaan. Lewerfunksietoetse behoort ook vir pasiënte uitgevoer te word as simptome wat op disfunksie van die lewer dui voorkom, bv. naarheid, braking, buikpyn, moegheid, anoreksie en donker urien. As ALT na 2,5 keer hoër as basislyn styg, behoort behandeling gestaak te word. As geelsug waargeneem word, behoort **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** onttrek te word.
Terapie met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** behoort nie begin te word nie as die pasiënt kliniese bewyse van aktiewe lewersiekte toon, of as die ALT-vlakke 2,5 keer die boonste vlak van normaal oorskry. Pasiënte met matig verhoogde lewerensiemvlakke (ALT 1 tot 2,5 keer hoër as die boonste limiet van normaal) teen basislyn of enige tyd gedurende terapie, behoort geëvalueer te word om die oorsaak van die lewerensiemverhoging vas te stel. Inisiëring van of voortsetting met terapie met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** in pasiënte met matig verhoogde lewerensieme behoort met die uiterste sorg voort te gaan en sluit die toepaslike kliniese opvolg, wat meer gereelde lewerensiemmonitering insluit, in. As serumtransaminasevlakke verhoog is (> 2,5 keer die boonste limiet van normaal), of as die pasiënt geelsug het, behoort **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** onttrek te word.

Hematologie:
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS mag afnames in hemoglobien en hematokrit veroorsaak. Gemiddelde hemoglobienwaardes het met 2 % tot 4 % in pioglitasoon behandelde pasiënte gedaal. Hierdie veranderinge het hoofsaaklik binne die eerste 4 tot 12 weke van terapie voorgekom en het relatief konstant daarna voortgeduur. Hierdie veranderinge mag verband hou met die toename in plasmavolume en kan nie noodwendig met enige beduidende hematologiese kliniese effekte geassosieer word nie.

Massatoename:
Dosisverwante massatoename is met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** alleen, asook in kombinasie met ander hipoglukemiemedisyne waargeneem. Die meganisme van massatoename is onduidelik, maar behels waarskynlik 'n kombinasie van vloeistofretensie en vetakkumulasie.

Makulêre edeem:
Die nuwe aanvang of agteruitgang van (diabetiese) makulêre edeem met 'n afname in visuele skerpheid is met die gebruik van **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** waargeneem. Mediese praktisyns behoort die moontlikheid van makulêre edeem te oorweeg as 'n pasiënt 'n afname in visuele skerpheid aanmeld.

Ander:
'n Toename in die voorkoms van beenfrakture in vroue is in pasiënte op behandeling vir tot so lank as 3,5 jare aangemeld.
Sommige epidemiologiese studies wil op 'n soortgelyke toename in risiko in beide mans en vroue dui.
Die risiko van frakture behoort in die langtermyn sorg van pasiënte wat met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** behandel word, oorweeg te word.

Dit is belangrik om pasiënte daarvan bewus te maak om by dieetinstruksies te bly en om hul bloedglukose en geglikosileerde hemoglobien gereeld te laat toets. Gedurende periodes van stres soos koors, trauma, infeksie of chirurgie mag die medikasiebehoeftes verander en pasiënte behoort herinner te word om dadelik mediese advies te kry.

Laboratoriumtoetse:
Lewerensiemmonitering is in alle pasiënte noodsaaklik vóór inisiëring van terapie met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS**, asook periodiek daarna. Pasiënte wat ongewoon vinnige massatoename of edeem ondervind, of wat kortasemheid of ander tekens van hartversaking ontwikkel terwyl hulle op **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** is, behoort onmiddellik hierdie simptome aan hulle dokters te rapporteer.
Pasiënte behoort in kennis gestel te word dat bloedtoetse vir lewerfunksie elke twee maande vir die eerste jaar en periodiek daarna uitgevoer sal word. Pasiënte behoort aangesê te word dat hulle onmiddellik mediese advies moet inwin wanneer hulle onverklaarde naarheid, braking, buikpyn, moegheid, edeem, anoreksie ondervind en donker urien waarneem.

Effek op die vermoë om te bestuur en masjinerie te gebruik:
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS het geen of 'n minimale invloed op die vermoë om te bestuur en masjinerie te gebruik nie. Pasiënte wat visuele afwykings ondervind behoort egter versigtig te wees wanneer hulle bestuur of masjinerie gebruik.

Laktosewaarskuwing:
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS bevat laktose. Pasiënte met seldsame voorkomende oorerflike kondisies van galaktose-intoleransie bv. galaktosemie, Lapp-laktasetekort, glukose-galaktose wanabsorpsie of fruktose-intoleransie behoort nie **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** te neem nie.
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS tablette bevat laktose wat 'n effek op glukemiebeheer in pasiënte met diabetes mellitus mag hê.

INTERAKSIES
Interaksies met ander middels
Orale voorbehoedmiddels:
Die toediening van 'n ander tiasolidinedioon met 'n orale voorbehoedmiddel wat etinielestradiol en noretindroon het die konsentrasie van beide hormone met ongeveer 30 % verminder, wat tot 'n verlies aan voorbehoeding mag lei. Die farmakokinetika van die medetoediening van pioglitasoon saam met orale voorbehoedmiddels is nie in pasiënte wat pioglitasoon en 'n orale voorbehoedmiddel gebruik, geëvalueer nie. Daarom behoort addisionele sorg ten opsigte van voorbehoeding geneem te word in pasiënte wat **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** saam met 'n orale voorbehoedmiddel gebruik.

Glipisied:
In gesonde vrywilligers het die medetoediening van pioglitasoon (45 mg een keer per dag) en glipisied (5 mg een keer per dag) vir sewe dae nie die platokonsentrasie farmakokinetika van glipisied verander nie.

Digoksien:
In gesonde vrywilligers het die medetoediening van pioglitasoon (45 mg een keer per dag) en digoksien (0,25 mg een keer per dag) vir sewe dae nie die platokonsentrasie farmakokinetika van digoksien verander nie.

Warfarien:
In gesonde vrywilligers het die medetoediening (45 mg een keer per dag) vir sewe dae en warfarien nie die platokonsentrasie farmakokinetika van warfarien verander nie. Boonop het pioglitasoon geen kliniese beduidende effek op protrombientyd wanneer dit aan pasiënte wat chroniese warfarienterapie ontvang, toegedien word nie.

Metformien:
In gesonde vrywilligers het die medetoediening van metformien (1000 mg) en pioglitasoon (45 mg) na sewe dae van pioglitasoon (45 mg een keer per dag) nie die farmakokinetika van 'n enkel dosis metformien verander nie. Die sitochroom P450 isovorm CYP3A4 is gedeeltelik verantwoordelik vir die metabolisme van pioglitasoon. Spesifieke formele farmakokinetiese interaksiestudies met pioglitasoon en ander medisyne wat deur hierdie ensiem gemetaboliseer word, soos eritromisien, kalsiumkanaalblokkeerders, kisapried, kortikosteroïede, siklosporien, HMG Ko-A reduktase-inhibeerders, takrolimus, triasolam, trimetreksaat, asook die inhiberende medisyne soos ketokonasool en itrakonasool is nie uitgevoer nie. *In vitro* wil dit voorkom asof ketokonasool die metabolisme van pioglitasoon beduidend inhibeer. Pasiënte wat ketokonasool saam met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** ontvang behoort meer dikwels vir glukemiebeheer geëvalueer te word

'n Inhibeerder van CYP2C8 (soos gemfibrosiel) mag die AOK van pioglitasoon vergroot en 'n induseerder van CYP2C8 (soos rifampisien) mag die AOK van pioglitasoon verlaag.

Daar word aangemeld dat die medetoediening van **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** saam met rifampisien tot 'n 54 % afname in die AOK van pioglitasoon lei. Die **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** dosis mag moontlik, gebaseer op die kliniese respons wanneer rifampisien saam toegedien word, aangepas moet word.

Daar is aangemeld dat die medetoediening van **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** saam met gemfibrosiel tot 'n 3-voudige toename in die AOK van pioglitasoon gelei het. Aangesien daar 'n potensiaal van dosisverwante newe-effekte met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** bestaan, mag 'n afname in die **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** dosis nodig wees wanneer dit saam met gemfibrosiel toegedien word.

SWANGERSKAP EN LAKTASIE
Die veiligheid en effektiwiteit van **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** in swangerskap en laktasie is nie vasgestel nie (sien KONTRA-INDIKASIES).

DOSIS EN GEBRUIKSAANWYSINGS
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS behoort een keer per dag met of sonder 'n maaltyd geneem te word.
Die bestuur van antidiabetiese terapie behoort geïndividualiseer te word.

Monoterapie
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS monoterapie in pasiënte wat nie voldoende met dieet en oefening gekontroleer word nie, mag met 15 mg of 30 mg een keer per dag geïnisieer word. Vir pasiënte wat onvoldoende op die aanvanklike dosis **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** reageer kan die dosis met inkremente tot 45 mg een keer per dag verhoog word. Vir pasiënte wat nie voldoende op monoterapie reageer nie, behoort kombinasieterapie oorweeg te word.

Kombinasieterapie
Sulfonielureums:
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS in kombinasie met sulfonielureums kan teen 15 mg tot 30 mg een keer per dag geïnisieer word. Die huidige sulfonielureumdosis kan voortgesit word met inisiëring van terapie met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS**. As pasiënte hipoglukemie aanmeld, behoort die sulfonielureumdosis verminder te word.

Metformien:
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS in kombinasie met sulfonielureums kan teen 15 mg tot 30 mg een keer per dag geïnisieer word. Met die inisiëring van **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** kan met die huidige metformiendosis voortgegaan word. Dit is onwaarskynlik dat die metformiendosis weens hipoglukemie gedurende kombinasieterapie met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** aangepas moet word.

Insulien:
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS in kombinasie met insulien kan teen 15 mg tot 30 mg een keer per dag geïnisieer word. Met die inisiëring van **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** kan daar met die huidige insulien dosis voortgegaan word. In pasiënte wat **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** en insulien ontvang, behoort die dosis **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** of die insulien dosis verminder te word as die pasiënt hipoglukemie aanmeld of as die plasmaglukosekonsentrasie na minder as 5,5 mmol/l (100 mg/dl) daal. Gebaseer op die glukoseverlagende respons behoort verdere aanpassings op 'n individuele basis te geskied.

Maksimum aanbevole dosis:
Aangesien dosisse van meer as 45 mg een keer per dag nie bestudeer is nie, behoort die **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** dosis nie 45 mg een keer per dag te oorskry nie. Geen studies met meer as 30 mg een keer per dag in kombinasieterapie is uitgevoer nie. Dosisaanpassing in pasiënte met onderwerkende nierfunksie word nie aanbeveel nie.
Terapie met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** behoort nie geïnisieer te word as die pasiënt kliniese tekens van aktiewe lewersiekte of 'n toename in serumtransaminase (ALT meer as 2,5 keer die boonste limiet van normaal) aan die begin van terapie toon nie. Die monitering van lewerensieme word in alle pasiënte vóór inisiëring van terapie met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** aanbeveel, asook periodiek daarna. Geen data is beskikbaar oor die gebruik van **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** in kombinasie met 'n ander tiasolidinedioon nie.

NEWE-EFFEKTE
Kliniese newe-effekte wanneer **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** in kombinasie met sulfonielureums, metformien of insulien gebruik is, was oor die algemeen soortgelyk aan dié wat met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** monoterapie aangemeld is, met die uitsondering van 'n toename in die voorkoms van geringe tot matige edeem in die insulien kombinasiestudie. Geringe tot matige hipoglukemie is gedurende kombinasieterapie met sulfonielureums of insulien aangemeld.

In na-bemarkingsondervinding met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** is kongestiewe hartversaking in pasiënte beide met en sonder reeds bestaande hartsiekte aangemeld. In na-bemarkingsondervinding met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** is gevalle van hepatitis en verhogings van lewerensieme van tot 3 keer hoër as die boonste limiet van normaal aangemeld. Dit het baie selde met lewerversaking, met en sonder fatale uitkoms gepaard gegaan. Geen oorsaaklikheid is egter vasgestel nie.

Sisteem orgaanklas/ Newe-effekte	Frekwensie van newe-effekte per behandelingsregimen				
	Mono-terapie	Kombinasieterapie met: Metformien	Sulfonielureum	Metformien en sulfonielureum	Insulien
Infeksies en infestasies					
Boonste lugweg-infeksie	Dikwels	Dikwels	Dikwels	Dikwels	Dikwels
Brongitis					Dikwels
Sinusitis	Minder dikwels	Minder dikwels	Minder dikwels	Minder dikwels	Minder dikwels
Benigne, kwaadaardige en ongespesifiseerde neo-plasmas					
Blaaskanker	Minder dikwels	Minder dikwels	Minder dikwels	Minder dikwels	Minder dikwels
Afwykings van die bloed- en limfsisteem					
Anemie		Dikwels			
Afwykings van die immuunstelsel					
Hipersensitiwiteit en allergiese reaksies	Frekwensie onbekend	Frekwensie onbekend	Frekwensie onbekend	Frekwensie onbekend	Frekwensie onbekend
Metaboliese en voedingsafwykings					
Hipoglukemie			Minder dikwels	Dikwels	Dikwels
Toename in eetlus			Minder dikwels		
Afwykings van die senuweestelsel					
Hipoëstesie	Dikwels	Dikwels	Dikwels	Dikwels	Dikwels
Hoofpyn		Dikwels	Minder dikwels		
Duiseligheid			Dikwels		
Slaaploosheid	Minder dikwels	Minder dikwels	Minder dikwels	Minder dikwels	Minder dikwels
Oogafwykings					
Visuele afwyking	Dikwels	Dikwels	Minder dikwels		
Afwykings van die oor en labirint					
Vertigo			Minder dikwels		
Hartafwykings					
Hartversaking					Dikwels
Respiratoriese, bors- en mediastinale afwykings					
Dispnee					Dikwels
Gastrointestinale afwykings					
Winderigheid		Minder dikwels	Dikwels		
Afwykings van die vel en subkutane weefsel					
Sweet			Minder dikwels		
Muskuloskeletale en bindweefsel-afwykings					
Beenfraktuur	Dikwels	Dikwels	Dikwels	Dikwels	Dikwels
Artralgie		Dikwels		Dikwels	Dikwels
Rugpyn					Dikwels
Nier- en urienafwykings					
Hematurie		Dikwels			
Glukosurie			Minder dikwels		
Proteïenurie			Minder dikwels		
Reproduksiestelsel- en borsafwykings					
Erektiele disfunksie		Dikwels			
Algemene afwykings en kondisies by die plek van toediening					
Edeem					
Moegheid			Minder dikwels		
Ondersoeke					
Massatoename	Dikwels	Dikwels	Dikwels	Dikwels	Dikwels
Toename in bloedkreatienfosfokinase				Dikwels	
Toename in melksuurdehidrogenase			Minder dikwels		
Toename in alanienaminotransferase	Frekwensie onbekend	Frekwensie onbekend	Frekwensie onbekend	Frekwensie onbekend	Frekwensie onbekend

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN
In die geval van oordosering behoort die toepaslike ondersteunende behandeling volgens die pasiënt se kliniese tekens en simptome toegepas te word.

IDENTIFIKASIE
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg:
Wit, ronde, plat, skuinskant, onbedekte tablet met 'ML86' op die een kant gedruk en ongedruk aan die ander kant nie.

PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 30 mg:
Wit, ronde, plat, skuinskant, onbedekte tablet met 'ML87' op die een kant gedruk en ongedruk aan die ander kant nie.

AANBIEDING
Kouevorm Alu/Alu stolpstrokie bestaande uit aluminiumfoelie gelamineer aan ge-oriënteerde poliamied aan een kant en gelamineer aan PVC as die vormingmateriaal aan die ander kant, met gewone aluminiumfoelie as die dekkingsmateriaal. Elke strokie bevat 10 tablette en 3 strokies word saam met 'n voubiljet in 'n karton verpak.
Grootmaat verpakking bestaan uit 'n wit plastiekhouer (HDPE), aan die mond geseël met aluminium en bedek met 'n HDPE skroefdeksel. Pakgroottes bestaan uit 30 tablette en 90 tablette.

BERGINGSINSTRUKSIES
Bewaar by of onder 30 °C in die oorspronklike houer. Beskerm teen vog en humiditeit. Die stolpstrokies moet tot voor gebruik in die karton gehou word. Hou die HDPE-houer toe.
HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMER
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg:
46/21.2/0257
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 30 mg:
46/21.2/0258

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE
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Kantoorblok 1, Bassonia Estate Kantoorpark (Oos)
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Suid Afrika

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INLIGTINGSBLAD VIR PASIËNTE

SKEDULERINGSTATUS

S3

EIENDOMSNAAM, STERKTE EN FARMASEUTIESE VORM
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg (tablet)
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 30 mg (tablet)

Lees die hele brosjure sorgvuldig voordat u begin om PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS te neem.
- Hou hierdie blaadjie. U mag dit moontlik weer wil lees
- Indien u enige verdere vrae het, moet u asseblief u dokter of apteker raadpleeg.
- **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** is vir u persoonlik voorgeskryf en u behoort nie u medisyne met ander mense te deel nie. Dit mag hulle skade aandoen, ook al het hulle dieselfde simptome.

WAT PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS BEVAT
Elke tablet bevat:
Pioglitasoonhidrochloried ekwivalent aan pioglitasoon 15 of 30 mg.
Ander bestanddele: Laktosemonohidraat, karboksimetielsellulose kalsium, hidroksipropielsellulose en magnesiumstearaat.
Bevat suiker (laktose).

WAARVOOR PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS GEBRUIK WORD
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS word gebruik om volwasse pasiënte met tipe 2 diabetes (ook nie-insulien afhanklike diabetes) in samewerking met 'n dieet- en oefeningsprogram te behandel om u bloedglukosevlakke te beheer. **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** kan alleen of saam met ander medisyne om diabetes te beheer (medisyne per mond geneem of insulien) geneem word wanneer dieet en oefening plus die enkel medisyne nie u bloedsuikervlakke voldoende beheer nie.

VOORDAT U PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS NEEM
MOENIE PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS neem nie:
- As u allergies teen pioglitasoon hidrochloried of enige van die bestanddele van **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** is.
- As u aan nier- of lewerprobleme ly.
- As u vir hartversaking behandel word of onlangs 'n hartaanval gehad het, of erge probleme met u sirkulasie (soos skok) het, of as u aan asemhalingsprobleme ly.
- As u aan onbeheerde diabetes, met erge hiperglukemie (hoë bloedglukose), naarheid, braking, dehidrasie, vinnige massaverlies of keto-asidose ly. Keto-asidose is 'n kondisie waartydens substanse nl. ketonliggaampies in die bloed versamel wat tot diabetiese pre-koma kan lei. Simptome sluit maagpyn, vinnige en diep asemhaling, slaperigheid en 'n ongewone vrugtegeur van die asem.
- As u aan blaaskanker ly of gely het.
- As u bloed in die urien het en u dokter dit nog nie ondersoek het nie.
- As u swanger is of borsvoed.

PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS behoort nie aan kinders gegee te word nie.

Neem spesiale sorg met PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS:
Stel u dokter in kennis:
- Oor enige vorige of huidige mediese probleme.
- Oor enige risikofaktore vir hartsiekte.
- As u 'n familiegeskiedenis van hartsiekte het.
- Oor enige allergieë wat u het of gehad het
- As u aan 'n nier- of lewersiekte ly.

Terwyl u PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS neem:
- Gaan voort met u oefenings- en dieetprogram en laat u bloedsuiker gereeld toets terwyl u **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** neem. U dokter sal u diabetes monitor en mag van tyd tot tyd bloedtoetse uitvoer om te verseker dat u niere en lewer normaal funksioneer.
- Monitor gereeld u bloedglukosevlakke as u **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** saam met ander antidiabetiese medisyne soos 'n sulfonielureum of insulien neem. As u **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** saam met ander medisyne vir diabetes neem, is dit meer waarskynlik dat u bloedsuiker laer as die normale vlak kan daal (hipoglukemie). U dokter mag moontlik die dosis van die ander medisyne verminder.
- As u 'n vrou is wat nie normaal ovuleer nie, bv. as u siste op u eierstokke (polisistiese ovariumsindroom) het, is daar 'n toename in die moontlikheid dat u weer mag begin ovuleer wanneer u **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** neem. As dit by u die geval is, moet u die toepaslike voorbehoeding gebruik om die moontlikheid van 'n onbeplande swangerskap te vermy.
- Sommige pasiënte wat al lank aan tipe 2 diabetes ly en bejaardes kan hartversaking ontwikkel terwyl hulle **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** neem. Stel u dokter so gou as moontlik in kennis as u tekens van hartversaking soos ongewone kortasemheid of 'n vinnige toename in massa of plaaslike swelling (edeem) ontwikkel
- Die gebruik van anti-inflammatoriese middels saam met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** kan tot hartversaking en vloeistofretensie en swelling lei. Stel u dokter onmiddellik in kennis as u enige tekens van vloeistofretensie of swelling ondervind.
- Blaaskanker is minder dikwels in pasiënte wat **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** neem, ondervind. Tekens en simptome sluit bloed in die urien, pyn tydens urinering of urienood in. As u enige van hierdie simptome ondervind moet u u dokter so gou as moontlik in kennis stel.
- Stel u dokter in kennis as u simptome van naarheid, braking, maagpyn, moegheid, verlies aan eetlus, donker urien of geel verkleuring van die vel (geelsug) ondervind. U dokter sal u lewer toets en mag moontlik die behandeling met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** staak.
- U mag 'n afname in bloedtelling (anemie) ondervind - met simptome van moegheid, hoofpyn, kortasemheid tydens oefening, vinnige hartklop, moeite om te konsentreer, duiseligheid, beenkrampe, moeite om aan die slaap te raak en bleekheid.
- **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** kan tot massatoename lei
- **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** kan tot onduidelike gesig lei weens swelling (of vloeistofaansameling) aan die agterkant van die oog. As u hierdie simptoom vir die eerste keer ondervind, moet u so gou as moontlik u dokter raadpleeg. As u reeds aan onduidelike gesig ly, en die simptoom raak erger, moet u so gou as moontlik u dokter daarvan in kennis stel.
- **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** kan beenfrakture in beide mans en vroue veroorsaak. Stel u dokter onmiddellik in kennis as u 'n beenfraktuur ondervind.

Die neem van PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS saam met voedsel en vloeistof:
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS kan met of sonder voedsel geneem word.

Swangerskap en borsvoeding:

As u swanger is of u baba borsvoed, moet u asseblief u dokter, apteker of ander professionele gesondheidswerker vir advies nader voordat u **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** neem.

PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS behoort nie gedurende swangerskap geneem te word nie.
Stel u dokter of apteker in kennis as u borsvoed of beplan om te borsvoed. **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** behoort nie geneem te word terwyl u borsvoed nie.

Bestuur en die gebruik van masjinerie:
As u simptome van hipoglukemie (lae bloedsuikervlakke met simptome van swakheid, duiseligheid, toename in sweet, vinnige hartklop, gesigsafwykings of moeite met konsentrasie ondervind terwyl u **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** neem, behoort u nie te bestuur of met masjinerie te werk nie.

Belangrike inligting oor sommige van die bestanddele van PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS:
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS bevat laktose. Pasiënte met die selde voorkomende oorerflike kondisies van laktose/fruktose- of galaktose-intoleransie behoort nie **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** te neem nie

Die neem van ander medisyne saam met PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS:

Stel altyd u professionele gesondheidswerker in kennis as u enige ander medisyne gebruik. Dit sluit komplimentêre of tradisionele medisyne in.

Neem slegs ander medisyne terwyl u op **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** is as u dokter dit goedkeur. Stel u dokter in kennis as u enige van die volgende medisyne neem:
- Gemfibrosiel (gebruik om cholesterol te verlaag).
- Rifampisien (gebruik om tuberkulose en ander infeksies te behandel).
- Orale voorbehoedmiddels (bykomende voorbehoedende maatreëls behoort getref te word terwyl u **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** gebruik).
- Anti-inflammatoriese medisyne saam met **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS**. Dit mag nodig wees om meer gereeld bloedglukosetoetse te ondergaan of u dokter mag besluit om die **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** dosis aan te pas.

HOE OM PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS TE NEEM

Moenie medisyne wat vir u voorgeskryf is met enigiemand anders deel nie. Neem **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** altyd presies soos deur u dokter voorgeskryf. Bevestig met u dokter of apteker as u onseker is. As u van mening is dat die effek van **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** te sterk of te swak is, moet u u dokter of apteker raadpleeg.

U dokter sal u in kennis stel oor hoeveel **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** om te neem en vir hoe lank u dit moet neem
Neem **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** met of na 'n maaltyd.
Moenie die tablette breek of kou nie. Sluk elke tablet met 'n glas water.
Die gewone aanvangsdosis is een tablet van 15 mg of 30 mg **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** wat een maal daagliks geneem moet word. Jou dokter kan die dosis tot 'n maksimum van 45 mg een keer per dag verhoog.

As u vergeet het om PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS te neem:
Dit is belangrik om die dosis **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** op dieselfde tyd elke dag te neem. As u vergeet het om 'n dosis **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** te neem, moet u dit sodra u daarvan onthou, neem. As dit agter byna tyd vir die volgende dosis is, slaan die oorgeslaande dosis oor en gaan met die gereelde doseringskedule voort. Moenie die dosis verdubbel om vir 'n oorgeslaande dosis op te maak nie

As u ophou om PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS te neem:
Moenie ophou om **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** te neem net omdat u beter voel nie. Dit is belangrik dat u aanhou om **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** te neem vir solank as wat u dokter dit voorskryf.

As u te veel PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS neem:

In die geval van oordosering, raadpleeg u dokter of apteker. As hulle nie beskikbaar is nie, kontak u naaste hospitaal of gifbeheersentrum.

MOONTLIKE NEWE-EFFEKTE
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS kan newe-effekte hê:
Nie al die newe-effekte wat vir **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** aangemeld is, word in hierdie brosjure ingesluit nie. As u algemene gesondheid agteruitgaan of as u enige ongewone effekte ondervind terwyl u **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** neem, moet u asseblief u dokter, apteker of ander professionele gesondheidswerker vir advies raadpleeg.

As enige van die volgende met u gebeur moet u met die gebruik van ***PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS*** *staak en onmiddellik u dokter raadpleeg of na die ongevalle-afdeling van u naaste hospitaal gaan:*
- Skielike tekens van allergie - insluitende veluitslag, jeuk of urtikarie, swelling van die gesig, lippe of tong, kortasemheid of moeite met asemhaling.
- Hartversaking. Stel u dokter so gou as moontlik in kennis as u tekens van hartversaking soos ongewone kortasemheid of 'n vinnige massatoename of plaaslike swelling (edeem) ondervind.
- Blaaskanker. Tekens en simptome sluit die volgende in: bloed in u urien, pyn tydens urinering, urienood. As u enige van hierdie simptome ondervind, moet u so gou as moontlik u dokter in kennis stel.

Die bogenoemde is almal ernstige newe-effekte wat minder dikwels voorkom. U het moontlik dringende mediese hulp of hospitalisering nodig.

As enige van die volgende gebeur, stel onmiddellik u dokter in kennis of gaan na die ongevalle-afdeling van u naaste hospitaal:
- Hipoglukemie - Lae suikervlakke (glukose) in die bloed, veral as u **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** saam met ander antidiabetiese medisyne soos 'n sulfonielureum of insulien neem. Simptome mag die volgende insluit: sweet, swakheid, bewerasie, hoofpyn, hittegloede of bleekheid, gevoelloosheid of vinnige, bonsende hartklop.
- Onduidelike gesig weens swelling (of vloeistof) aan die agterkant van die oë.
- Abnormale lewerfunksietoetse of hepatitis (inflammasie van die lewer: dit mag moegheid, verlies aan eetlus, massaverlies met of sonder geel verkleuring van die vel of oë). As dit gebeur, moet u met die gebruik van **PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS** ophou en u dokter in kennis stel.
- Beenfraktura.

Stel u dokter in kennis as u enige van die volgende waarneem:
Dikwels voorkomende newe-effekte:
- asemhalingsinfeksie
- gevoelloosheid
- hoofpyn
- duiseligheid
- onduidelike gesig
- kortasemheid
- afname in die rooibloedselteling (anemia)
- winderigheid
- gewrigspyn
- rugpyn
- bloed in die urien
- impotensie
- swelling van die arms en bene (edeem)
- massatoename

Minder dikwels voorkomende newe-effekte:
- inflammasie van die sinusse (sinusitis)
- toename in eetlus
- draaigevoel (vertigo)
- sweet
- moegheid (please check english copy - duplication)
- laboratoriumtoetse mag die volgende toon: suiker in die urien, proteïene in die urien, toename in ensieme.

OPBERGING EN WEGDOEN VAN PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS
Bewaar by of onder 30 °C (kamertemperatuur) in die oorspronklike houer. Beskerm teen vog en humiditeit. Die stolpstrokies moet tot voor gebruik in die karton gehou word. Hou die HDPE-houer toe.
HOU ALLE MEDISYNE BUITE BEREIK VAN KINDERS.

Neem alle ongebruikte medisyne na u apteker terug. Moenie ongebruikte medisyne in die riolering (bv. toilet) wegdoen nie

AANBIEDING
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS
Kouevorm Alu/Alu stolpstrokie bestaande uit aluminiumfoelie gelamineer aan ge-oriënteerde poliamied aan een kant en gelamineer aan PVC as die vormingmateriaal aan die ander kant, met gewone aluminiumfoelie as die dekkingsmateriaal. Elke strokie bevat 10 tablette en 3 strokies word saam met 'n voubiljet in 'n karton verpak.
Grootmaat verpakking bestaan uit 'n wit plastiekhouer (HDPE), aan die mond geseël met aluminium en bedek met 'n HDPE skroefdeksel. Pakgroottes bestaan uit 30 tablette en 90 tablette.

IDENTIFIKASIE
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg:
Wit, ronde, plat, skuinskant, onbedekte tablet met 'ML86' op die een kant gedruk en ongedruk aan die ander kant nie.
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 30 mg:
Wit, ronde, plat, skuinskant, onbedekte tablet met 'ML87' op die een kant gedruk en ongedruk aan die ander kant nie.

REGISTRASIENOMMER
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg:
46/21.2/0257
PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 30 mg:
46/21.2/0258

NAAM EN BESIGHEIDSADRES VAN DIE REGISTRASIEHOUER
MACLEODS PHARMACEUTICALS SA (EDMS) BPK
Kantoorblok 1, Bassonia Estate Kantoorpark (Oos)
Cussonialryaan 1, Bassonia Rock, Uitbr. 12, Alberton
Suid Afrika

DATUM VAN PUBLIKASIE
20 Maart 2018

MASTER COPY

MACLEODS

PACKAGING RESEARCH & DEVELOPMENT

Restricted Circulation

(Front Page)

ARTWORK / PRINTPROOF APPROVAL FORM

1. Product: PIOGLITAZONE HYDROCHLORIDE TABLETS MACLEODS 15 mg / 30 mg	
2. Country: South Africa	3. Packaging component: Package insert & Patient Information Leaflet
4. No. of Colours: 1 Colour	5. Pantone Shade No.: Black
6. Specification: 40 gsm bible paper	
7. Machine Layout No.: NA	8. Dimensions: 435 x 490 mm
9. Design / Style: Booklet type	10. Item code No.: PM02864001
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10/10/18	Shehaboodeen Chorfany	10/10/18	15/10/18	15/10/18	15/10/18

Note: 1. To follow overleaf checklist for approval of Artwork / Print proof.

Instructions to Vendor :

1. Before processing, please ensure First pull out / Commercial supply should match with approved Artwork with respect to Design, Size, Fonts & Text.
2. Print proof to represent full printing area with Station Numbers.

FRM/CQA/021/04-01

Reason for revision :	Item code	Artwork Release Date	Artwork Implementation Date
1) New Artwork for South Africa	PM02864001		

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