ACTOS® Tablet
PIOGLITAZONE 15 & 30 mg

DESCRIPTION

ACTOS Tablet 15 mg :
The tablets are, white, round and marked “15“ on one side containing 15 mg Pioglitazone (16.53 mg Pioglitazone hydrochloride).

ACTOS Tablet 30 mg :
The tablets are white, round, marked “30” on one side and scored on the other side, containing 30 mg Pioglitazone (33.06 mg Pioglitazone hydrochloride).

PHARMACOLOGICAL ACTIONS

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

Fasting and postprandial glycaemic control is improved in patients with type 2 diabetes mellitus. The improved glycaemic control is associated with a reduction in both fasting and postprandial plasma insulin concentration. A clinical trial of pioglitazone vs. gliclazide as monotherapy was extended to two years in order to assess time to treatment failure (defined as appearance of $HbA_{1c} \geq 8.0$ % after the first six months of therapy). Kaplan-Meier analysis showed shorter time to treatment failure in patients treated with gliclazide, compared with pioglitazone. At two years, glycaemic control (defined as $HbA_{1c} < 8.0$ %) was sustained in 69 % of patients treated with pioglitazone, compared with 50 % of patients on gliclazide. In a two-year study of combination therapy comparing pioglitazone with gliclazide when added to metformin, glycaemic control measured as mean change from baseline in HbA_{1c} was similar between treatment groups after one year. The rate of deterioration of HbA_{1c} during the second year was less with pioglitazone than with gliclazide.

HOMA analysis shows that pioglitazone improves beta cell function as well as increasing insulin sensitivity.
Two-year clinical studies have shown maintenance of this effect.

In one year clinical trials, pioglitazone consistently gave a statistically significant reduction in the albumin/creatinine ratio compared to baseline.

The effect of pioglitazone (45 mg monotherapy *vs.* placebo) was studied in a small 18-week trial in type 2 diabetics. Pioglitazone was associated with significant weight gain. Visceral fat was significantly decreased, while there was an increase in extra-abdominal fat mass. Similar changes in body fat distribution on pioglitazone have been accompanied by an improvement in insulin sensitivity. In most clinical trials, reduced total plasma triglycerides and free fatty acids, and increased HDL-cholesterol levels were observed as compared to placebo, with small, but not clinically significant increases in LDL-cholesterol levels.

In clinical trials of up to two years duration, pioglitazone reduced total plasma triglycerides and free fatty acids, and increased HDL cholesterol levels, compared with placebo, metformin or gliclazide. Pioglitazone did not cause statistically significant increases in LDL cholesterol levels compared with placebo, whilst reductions were observed with metformin and gliclazide. In a 20-week study, as well as reducing fasting triglycerides, pioglitazone reduced post prandial hypertriglyceridaemia through an effect on both absorbed and hepatically synthesised triglycerides. These effects were independent of pioglitazone’s effects on glycaemia and were statistically significant different to glibenclamide.

PRECLINICAL SAFETY DATA

In toxicology studies, plasma volume expansion with haemodilution, anaemia and eccentric cardiac hypertrophy was consistently apparent after repeated dosing of mice, rats, dogs, and monkeys. In addition, increased fatty deposition and infiltration were observed. These finding were observed across species at plasma concentrations < 4 times the clinical exposure. Foetal growth restriction was apparent in animal studies with ACTOS. This was attributable to the action of ACTOS in diminishing the maternal hyperinsulinaemia and increased resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth.

The formation and presence of urinary calculi with subsequent irritation and hyperplasia was postulated as the mechanistic basis for the observed tumourigenic response in the male rat. A 24-month mechanistic study in male rats

demonstrated that administration of pioglitazone resulted in an increased incidence of hyperplastic changes in the bladder. Dietary acidification significantly decreased but did not abolish the incidence of tumours. The presence of microcrystals exacerbated the hyperplastic response but was not considered to be the primary cause of hyperplastic changes. The relevance to humans of the tumourigenic findings in the male rat cannot be excluded.

ACTOS was devoid of genotoxic potential in a comprehensive battery of *in vivo* and *in vitro* genotoxicity assays. An increased incidence of hyperplasia (males and females) and tumors (males) of the urinary bladder epithelium was apparent in rats treated with ACTOS for up to 2 years. The relevance of this finding for human is unknown. There was no tumorigenic response in mice of either sex. Hyperplasia of the urinary bladder was not seen in dogs or monkeys treated for up to 12 months.

In an animal model of FAP (Familial Adenomatous Polyposis), treatment with two other thiazolidinediones increased tumor multiplicity in the colon. The relevance of this finding in human is unknown.

PHARMACOKINETIC PROPERTIES

Absorption :

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

Distribution :

The estimated volume of distribution in human is 0.25 l/Kg.

ACTOS and all active metabolites are extensively bound to plasma protein (> 99%).

Metabolism :

ACTOS undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 3A4 and 2C9 although multiple other isoforms are involved to a lesser degree. Three of the six identified metabolites are active (M-II, M-III, and M-IV).

When activity, concentrations and protein binding are taken into account, ACTOS and metabolite M-III contribute equally to efficacy. On this basis M-IV contribution to efficacy is approximately three-fold that of ACTOS, whilst the relative efficacy of M-II is minimal.

Elimination :

Following oral administration of radiolabelled pioglitazone to man, recovered label was mainly in faeces (55%) and a lesser amount in urine (45%). In animals, only a small amount of unchanged pioglitazone in man is 5 to 6 hours and for its total active metabolites 16 to 23 hours.

Elderly :

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

Patients with Renal Impairment :

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

Patients with Hepatic Impairment :

Total plasma concentration of ACTOS is unchanged, but with an increased volume of distribution. Intrinsic clearance is therefore reduced, coupled with a higher unbound fraction of ACTOS.

INDICATIONS

ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes.

<u>Monotherapy</u>

ACTOS is indicated for monotherapy.

<u>Dual Combination therapy</u>

ACTOS is indicated for use in combination with a sulfonylurea or metformin when diet and exercise plus the single agent does not result in adequate glycemic control.

Triple combination therapy
ACTOS is indicated for use in combination with metformin and a sulfonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

DOSAGE AND ADMINISTRATION
Method of Administration :
ACTOS tablets are taken orally once daily with or without food.

Dosage :
For Adult :

Monotherapy
Starting dose 15 mg or 30 mg once daily.
The dose can be increased in increments up to 45 mg once daily.

Combination therapy
Metformin :
ACTOS 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 ACTOS therapy.

Sulfonylurea :
ACTOS 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 ACTOS therapy. If patients report hypoglycemia, the dose of the Sulfonylurea should be decreased.

Elderly :
No dosage adjustment is necessary for elderly patients.

Patients with Renal Impairment :
No dosage adjustment is necessary in patients with impaired renal function (creatinine clearance > 4 ml/min).
No information is available from dialysed patients therefore ACTOS should not be used in such patients.

Patients with Hepatic Impairment :
ACTOS should not be used in patients with hepatic impairment.

Children and Adolescents :
There are no data available on the use of ACTOS in patients under 18 years, and therefore ACTOS is not recommended in this age group.

CONTRAINDICATION
ACTOS is contraindicated in patients with :
- Known hypersensitive to ACTOS or any of the excipients of the tablet
- Cardiac failure or history of cardiac failure (NYHA stages I to IV)
- Hepatic impairment
- Diabetic ketoacidosis
- Current bladder cancer or a history of bladder cancer
- Uninvestigated macroscopic haematuria

UNDESIRABLE EFFECTS

Tabulated List Of Adverse Reactions

Adverse reactions reported in excess (>0.5%) of placebo and as more than an isolated case in patients receiving pioglitazone in double-blind studies are listed below as MedDRA preferred term by system organ class and absolute frequency.
Frequencies are defined as : very common (≥ 1/10); common > 1/100 ; uncommon >1/1000, <1/100; rare >1/10000, <1/1000; very rare <1/10000; not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reaction	Frequency of adverse reactions of pioglitazone by treatment regimen			
	Mono therapy	Combination		
		With metformin	With sulphonyl-urea	With metformin and sulphonyl-urea
Infections and infestations				
upper respiratory tract infection	common	common	common	common
sinusitis	uncommon	uncommon	uncommon	uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
bladder cancer	uncommon	uncommon	uncommon	uncommon
Blood and lymphatic system disorders				
anaemia		common		
Immune System Disorders				
Hypersensitivity and allergic reactions[1]	not known	not known	not known	not known
Metabolism and nutrition disorders				
hypo-glycaemia			uncommon	very common
appetite increased			uncommon	
Nervous system disorders				
hypo-aesthesia	common	common	common	common
headache		common	uncommon	
dizziness			common	
insomnia	uncommon	uncommon	uncommon	uncommon
Eye disorders				
Visual disturbance[2]	common	common	uncommon	
macular oedema	not known	not known	not known	not known
Ear and labyrinth disorders				
vertigo			uncommon	
Gastrointestinal disorders				
flatulence		uncommon	common	
Skin and subcutaneous tissue disorders				
sweating			uncommon	
Musculoskeletal and connective tissue disorders				
fracture bone[4]	common	common	common	common
arthralgia		common		common
back pain				
Renal and urinary disorders				
haematuria		common		
glycosuria			uncommon	
proteinuria			uncommon	
Reproductive system and breast disorders				
erectile dysfunction		common		
General disorders and site conditions				
fatigue			uncommon	

Investigations				
weight increased[6]	common	common	common	common
blood creatine phospho-kinase increased				common
increased lactic dehydro-genase			uncommon	
alanine aminotransferase increased[7]	not known	not known	not known	not known

Description of selected adverse reactions

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

Oedema was reported in 6-9% of patients treated with pioglitazone over one year in controlled clinical trials. The oedema rates for comparator groups (sulfonylurea, metformin) were 2-5%. The reports of oedema were generally mild to moderate and usually did not require discontinuation of treatment.[5]

In active comparator controlled trials mean weight increase with pioglitazone given as monotherapy was 2-3 kg over one year. This is similar to that seen in a sulfonylurea active comparator group. In combination trials pioglitazone added to metformin resulted in mean weight increase over one year of 1.5 kg and added to a sulfonylurea of 2.8 kg. In comparator groups addition of sulfonylurea to metformin resulted in a mean weight gain of 1.3 kg and addition of metformin to a sulfonylurea a mean weight loss of 1.0 kg.[6]

Visual disturbance has been reported mainly early in treatment and is related to changes in blood glucose due to temporary alteration in the turgidity and refractive index of the lens as seen with other hypoglycaemic treatments.[2]

In clinical trials with pioglitazone the incidence of elevations of ALT greater than three times the upper limit of normal was equal to placebo but less than that seen in metformin or sulfonylurea comparator groups. Mean levels of liver enzymes decreased with treatment with pioglitazone. Rare cases of elevated liver enzymes and hepatocellular dysfunction have occurred in post-marketing experience. Although in very rare cases fatal outcome has been reported, causal relationship has not been established. [7]

A pooled analysis was conducted of adverse event reports of bone fractures from randomized, comparator controlled, double blind clinical trials in over 8100 patients in the pioglitazone-treated groups and 7400 in the comparator-treated groups of up to 3.5 years duration. A higher rate of fractures was observed in women taking pioglitazone (2.6%) versus comparator (1.7%). No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).
In the 3.5 year PROactive study, 44/870 (5.1%) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).
Postmarketing, bone fractures have been reported in both male and female patients.4

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluid Retention and Cardiac Failure :
Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction or symptomatic coronary artery disease), physicians should start with the lowest available dose and increase the dose gradually. Patients should be observed for signs and symptoms of heart failure, weight gain or edema particularly those with reduced cardiac reserve.
Post marketing cases of peripheral oedema and cardiac failure have also been reported in patients with concomitant use of pioglitazone and nonsteroidal anti-inflammatory drugs, including selective COX-2 inhibitors. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

A cardiovascular outcome study of pioglitazone has been performed in patients under 75 years with type 2 diabetes mellitus and pre-existing major macrovascular disease. Pioglitazone or placebo was added to existing antidiabetic and

cardiovascular therapy up to 3.5 years. This study showed an increase in reports of heart failure, however this did not lead to an increase in mortality in this study.

Bladder cancer
Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12506 patients, 0.15%) than in control groups (7 cases from 10212 patients, 0.07%) HR=2.64 (95% CI 1.11-6.31, P=0.029). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Epidemiological studies have also suggested a small increased risk of bladder cancer in diabetic patients treated with pioglitazone, although not all studies identified a statistically significant increased risk.
Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region).
Any macroscopic haematuria should be investigated before starting pioglitazone therapy. Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment. Patients who received pioglitazone more than one year, should be evaluated periodically for bladder cancer risk by urinalysis.

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

Following initiation of therapy with ACTOS, it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3 x upper limit of normal during ACTOS therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with ACTOS should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

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

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

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

Eye disorders:

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

Others :
An increased incidence in bone fractures in women was seen in a pooled analysis of adverse reactions of bone fracture from randomized, controlled, double blind clinical trials in over 8100 pioglitazone and 7400 comparator treated patients, on treatment for up to 3.5 years.
Fractures were observed in 2.6% of women taking pioglitazone compared to 1.7% of women treated with a comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).
The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this dataset on pioglitazone is therefore 0.8 fractures per 100 patient years of use.
In the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%; 1.0 fractures per 100 patient years) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures per 100 patient years) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).
Some epidemiological studies have suggested a similarly increased risk of fracture in both men and women.
The risk of fractures should be considered in the long term care of patients treated with pioglitazone.

As a consequence of enhancing insulin action, ACTOS treatment in patients with polycystic ovarian syndrome may result in resumption of ovulation. These patients may be risk of pregnancy. Patients should be aware of the risk of pregnancy and if a patient wishes to become pregnant or if pregnancy occurs the treatment should be discontinued.
Pioglitazone should be used with caution during concomitant administration of cytochrome P450 2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin). Glycaemic control should be monitored closely. Pioglitazone dose adjustment within the recommended posology or changes in diabetic treatment should be considered.
The tablets contain lactose monohydrate and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

FERTILITY, PREGNANCY AND LACTATION
Use in Pregnancy.
There are no adequate human data to determine the safety of pioglitazone during pregnancy. Foetal growth restriction was apparent in animal studies with ACTOS. This was attributable to the action of ACTOS in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth.
The relevance of such a mechanism in humans is unclear and ACTOS should not be used in pregnancy.

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

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No effects on ability to drive and use machines have been observed. However patients who experience visual disturbance should be cautious when driving or using machines.

DRUG INTERACTIONS
Interaction with other medicinal products and other forms of interaction
Interaction studies have shown that ACTOS has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Co-administration of ACTOS with sulfonylurea does not appear to affect the pharmacokinetics of the sulfonylurea.
Studies in man suggest no induction of the main inducible cytochrome P450, 1A, 2C8/9 and 3A4. *In vitro* studies have shown no inhibition of any subtype of Cytochrome P450. Interactions with substances metabolised by these enzymes, e.g. oral contraceptives, cyclosporin, calcium channel blocker , and HMGCoA reductase inhibitors are not to be expected.

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

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

OVERDOSE
In clinical studies, patients have taken pioglitazone at higher than the recommended highest dose of 45 mg daily. The maximum reported dose of 120 mg/day for four days, then 180 mg/day for seven days was not associated with any symptoms. Hypoglycaemia may occur in combination with sulfonylurea. Symptomatic and general supportive measures should be taken in case of overdose.

STORAGE
Store below 30°C (Protect from light and humidity).

SHELF LIFE
3 years.

PACKAGE
Actos 15 mg
Box 14 Tablets (2 Blisters @ 7 Tablets).

Actos 30 mg
Box 14 Tablets (2 Blisters @ 7 Tablets).

REGISTRATION NUMBER
15 mg, DKL0125102110A1
30 mg, DKL0125102110B1

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured by PT. Takeda Indonesia, Bekasi, Indonesia
Under licence of Takeda Pharmaceutical Company Limited, Osaka, Japan

BROSUR: INFORMASI BAGI PASIEN

Actos 15mg, 30 mg
Pioglitazone

Baca brosur ini dengan seksama sebelum Anda mulai menggunakan obat ini.

- Simpan brosur ini, mungkin diperlukan untuk dibaca kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, hubungi dokter atau apoteker Anda.
- Bila Obat ini telah diresepkan untuk Anda, jangan diberikan kepada orang lain karena akan membahayakannya, walaupun gejala mereka sama dengan gejala pada Anda.
- Jika terjadi efek samping yang serius, atau jika Anda menderita efek samping yang tidak tercantum dalam brosur, silakan hubungi dokter arau apoteker Anda.

Informasi yang tercantum pada brosur:

1. APAKAH TABLET PIAGLITAZONE ITU DAN BAGAIMANA PENGGUNAANNYA

ACTOS tablet mengandung piaglitazone. ACTOS diindikasikan sebagai pengobatan tambahan pada diet dan olahraga dalam memperbaiki kontrol gula darah pasien dengan diabetes tipe 2.
ACTOS dapat digunakan sebagai kombinasi dengan sulfonylurea atau metformin, apabila diet dan olahraga dan pengobatan tunggal tidak dapat mengontrol kadar gula dalam darah dengan baik.
ACTOS juga dapat digunakan sebagai kombinasi dengan sulfonylurea dan metformin, terutama pada pasien yang mengalami kelebihan berat badan dengan kontrol gula darah yang tidak mencukupi walaupun telah menggunakan kombinasi 2(dua) obat.
Piaglitazone membantu mengontrol kadar gula darah dengan menurunkan resistensi insulin.
Dokter Anda akan memeriksa apakah piaglitazone masih bekerja setelah 3 sampai 6 bulan terhitung sejak awal mula pemberian obat.

2. SEBELUM ANDA MENGGUNAKAN TABLET PIOGLITAZONE

Jangan mengkonsumsi tablet pioglitazone

- Bila Anda hipersensitif (alergi) terhadap pioglitazone atau terhadap salah satu bahan tambahan pada pioglitazone tablet.
- Bila Anda menderita gagal jantung atau pernah mengalami gagal jantung.
- Jika Anda menderita penyakit hati.
- Jika Anda pernah menderita diabetes ketoasidosis (suatu komplikasi penyakit diabetes yang menyebabkan penurunan berat badan dengan cepat, mual atau muntah).
- Jika anda penderita atau pernah menderita penyakit kanker kandung kemih.
- Jika dijumpai darah dalam urin dan belum diperiksa oleh dokter Anda.

Perhatian pada pemberian tablet pioglitazone

- Sebelum mengkonsumsi tablet pioglitazone informasikan kepada dokter Anda, jika Anda mengalami oedem (retensi urin) atau mengalami kegagalan jantung, terutama jika Anda berumur diatas 75 tahun.
- Jika Anda menderita penyakit diabetes yang menyerang mata, penyakit yang disebut macula edema (pembengkakan pada bagian belakang mata).

- Jika Anda memiliki kista pada ovarium (sindroma avarium polikistik) kemungkinan dapat hamil lagi karena dapat berovulasi lagi. Jika kemungkinan hal ini akan terjadi pada Anda, gunakan kontrasepsi yang sesuai untuk menghindari terjadinya kehamilan yang tidak diinginkan.
- Jika Anda memiliki masalah dengan hati atau jantung Anda, sebelum terapi dengan pioglitazone dimulai, sebaiknya diambil sampel darah untuk pemeriksaan fungsi hati. Pemeriksaan ini dapat diulang selang interval waktu tertentu.
- Beberapa pasien diabetes tipe 2 dengan penyakit hati atau sebelumnya pernah menderita stroke yang diterapi dengan pioglitazone dan insulin dapat memperberat penyakit kerusakan hati. Segera informasikan dokter Anda jika Anda mengalami gejala-gejala penyakit kegagalan hati berupa sesak nafas atau terjadi peningkatan berat badan dengan cepat atau pembengkakan (edema) jika Anda mengkonsumsi pioglitazone yang digabung dengan obat antidiabetes lain, kemungkinan kadar gula darah anda akan jauh dibawah normal (hipoglikemia)
  Anda mungkin juga mengalami pengurangan sel darah (anemia).

Tulang Keropos
Pada wanita yang mengkonsumsi pioglitazone dapat menderita tulang keropos (tidak terjadi pada pria) dokter anda akan mempertimbangkan hal ini dalam mengobati penyakit diabetes.

Pengunaan pada anak-anak
Tidak dianjurkan pengunaannya pada anak-anak dibawah umur 18 tahun.

Penggunaan bersamaan dengan obat lain
Informasikan ke dokter atau apoteker anda bila anda sedang menelan obat lain termasuk obat bebas.
Anda dapat melanjutkan mengkonsumsi obat lain, ketika sedang diterapi dengan pioglitazone.
Beberapa obat-obatan yang dapat mempengaruhi kadar gula darah:
- gemfribozil (menurunkan kolesterol)
- rifampisin (untuk pengobatan tuberkulosis dan infeksi lainnya)
Informasikan ke dokter atau apoteker bila anda sedang mengkonsumsi obat tersebut diatas. Kadar gula darah anda akan diperiksa dan dosis pioglitazone akan disesuaikan.

Penggunaan pioglitazone bersamaan dengan makanan dan minuman
Anda dapat menelan tablet pioglitazone dengan atau tanpa makanan. Anda dapat menelan tablet menggunakan segelas air.

Kehamilan dan menyusui
Informasikan ke dokter anda jika:
- Sedang hamil atau berencana akan hamil
- Sedang menyusui bayi atau berencana untuk menyusui bayi,
Dokter anda akan menganjurkan untuk berhenti mengkonsumsi obat ini.

Mengemudi dan menjalankan mesin
Pemberian Pioglitazone tidak mempengaruhi kemampuan mengemudi atau masih dapat menjalankan mesin, tetai hati-hati jika anda merasakan adanya gangguan penglihatan.

Informasi penting tentang bahan tambahan pada tablet pioglitazone
Obat ini mengandung laktosa monohidrat. Bila dokter telah menginformasikan bahwa Anda intolerans terhadap beberapa gula, hubungi dokter Anda sebelum mengkonsumsi tablet pioglitazone.

3. BAGAIMANA CARA MENGKONSUMSI TABLET PIOGLITAZONE

Satu tablet Pioglitazone 15 dan 30 mg diberikan sekali sehari, Bila perlu dokter akan memberikan anda dosis yang berbeda.
Dokter Anda mungkin meningkatkan dosis untuk maksimal 45 mg sekali sehari.Bila perlu dokter akan memberikan anda dosis yang berbeda.
Jika anda merasa bahwa efek pioglitazone terlalu ringan, informasikan ke dokter anda.

Ketika pioglitazone harus dikombinasikan dengan obat lain untuk pengobatan diabetes (seperti insulin, klorpropamid, glibenklamid, tolbutamide, gliclazid)
Dokter akan menginformasikan bahwa anda memerlukan pioglitazone dengan dosis yang lebih rendah.

Selama pengobatan dengan pioglitazone dokter akan menganjurkan Anda untuk melakukan pemeriksaan darah secara berkala untuk memastikan bahwa hati anda berfungsi dengan normal.

Jika Anda sedang mengikuti program diet diabetes, dianjurkan untuk melanjutkannya selama menjalani pengobatan dengan pioglitazone.

Dianjurkan untuk memeriksa berat badan secara teratur, jika terjadi peningkatan berat badan informasikan kedokter Anda.

Jika Anda mengkonsumsi pioglitazone dengan dosis berlebih
Jika tanpa sengaja tablet pioglitazone tertelan lebih banyak, atau jika orang lain atau anak anda menelan obat pioglitazone, segera hubungi dokter atau apoteker anda. Kadar gula darah anda dapat turun jauh dibawah normal dan dapat ditingkatkan kembali dengan mengkonsumsi gula, sehingga dianjurkan agar selalu membawa gula,permen atau jus buah berasa manis.

Jika Anda lupa menelan tablet pioglitazone
Dianjurkan untuk mengkonsumsi pioglitazone setiap hari sesuai dengan dosis yang dianjurkan. Namun jika Anda lupa meminum obatnya, lanjutkan minum obat dengan dosis seperti biasa, jangan meningkatkan dosisnya untuk mengganti tablet yang lupa ditelan.

Jika Anda berhenti mengkonsumsi pioglitazone
Tablet pioglitazone harus ditelan setiap hari agar pioglitazone dapat bekerja maksimal. Jika anda berhenti mengkonsumsinya kadar gula darah akan meningkat. Diskusikan hal ini dengan dokter anda sebelum berhenti mengkonsumsi obat ini.

Jika Anda membuthkan informasi lebih lanjut yang berhubungan dengan penggunaan obat ini, tanyakan kepada dokter atau apoteker anda.

4. EFEK SAMPING YANG MUNGKIN TERJADI

Sama seperti obat lainnya, penggunaan tablet pioglitazone dapat menimbulkan efek samping, walaupun tidak terjadi pada semua orang.

Pasien yang pernah mengalami efek samping yang serius:

Kanker kandung kemih dapat terjadi walaupun jarang (1 dari 100) pasien yang menelan tablet pioglitazone. Gejala seperti adanya darah didalam urine, nyeri pada saat buang air kecil, atau mendadak sering merasa akan buang air kecil. Bila anda merasakan salah satu dari gejala ini segera hubungi dokter yang bersangkutan.

Tulang keropos dapat terjadi (1 dari 10) pasien wanita yang menggunakan pioglitazone dan juga dilaporkan pada pasien pria (frekuensi tidak dapat diestimasi dari data yang tersedia). Jika anda merasakan efek samping ini segera hubungi dokter anda.

Penglihatan kabur disebabkan karena oedema atau adanya cairan dibelakang mata, dilaporkan pernah terjadi pada pasien yang diterapi dengan pioglitazone, Jika anda merasakan gejala ini pertama kali segera hubungi dokter anda, juga bila pandangan anda semakin kabur, segera informasikan ke dokter anda sesegera mungkin.

Reaksi alergi telah dilaporkan (frekuensi tidak dapat diperkirakan dari data yang tersedia) pada pasien yang diterapi dengan pioglitazone. Jika Anda memiliki reaksi alergi yang serius, termasuk gatal-gatal dan pembengkakan wajah, bibir, lidah, atau tenggorokan yang dapat menyebabkan kesulitan bernafas atau menelan. berhenti minum obat ini dan informasikan ke dokter anda sesegera mungkin.

Efek samping lain yang pernah dialami oleh pasien-pasien yang mengkonsumsi pioglitazone adalah:
Umumnya terjadi (pada 1 dari 10 pasien):
- Infeksi saluran nafas
- Gangguan penglihatan
- Perubahan berat badan
- Mati rasa

Kadang – kadang dapat terjadi (1 dari 10 pasien):
- Peradangan sinus (sinusistis)
- Gangguan tidur (insomnia)

Sangat jarang terjadi:
- Peningkatan enzim hati
- Reaksi alergi

Efek samping lain yang pernah terjadi pada pasien yang di terapi dengan kombinasi pioglitazone dengan antidiabetes lain:

Umumnya terjadi (1 dari 10)
-Penurunan kadar gula darah (hypoglikemia)

Biasanya terjadi: (1 dari 10)
- Sakit kepala
- Pusing
- Nyeri sendi
- Impotent
- Nyeri punggung
- Sesak nafas
- Penurunan jumlah sel darah merah
- Kembung

Jarang terjadi (1 dari 100)
- Terdapat gula atau protein diurin
- peningkatan kadar enzim
- Pusing (vertigo)
- Berkeringat
- Letih

- Nafsu makan meningkat

Bila mengalami efek samping yang serius atau terjadi efek samping yang tidak tercantum pada brosur, hubungi dokter atau apoteker anda.

5. BAGAIMANA CARA PENYIMPANAN TABLET PIOGLITAZONE

Jauhkan obat ini dari jangkauan anak – anak

Jangan mengkonsumsi tablet yang sudah kadaluarsa seperti yang tertera pada box dan blister setelah kata << EXP. Tanggal kadaluarsa merupakan hari terakhir pada bulan tersebut.

Tidak diperlukan kondisi khusus unutk menyimpan obat ini.

Jangan membuang obat di air limbah atau dilimbah rumah tangga. Tanyakan ke apoteker Anda bagaimana membuang obat yang sudah tidak dapat digunakan lagi.
Langkah ini dilakukan untuk membantu memelihara lingkungan.

6. INFORMASI LEBIH JAUH

Apa saja kandungan tablet pioglitazone
- Bahan baku aktifnya adalah pioglitazone. Tiap tablet mengandung pioglitazone 15 atau 30 mg (dalam bentuk hydrochloride)
- Bahan tambahan lainya adalah lactose monohidrat, hyprolose, carmellose calsium dan magnesium stearate.

Bagaimana bentuk dan kemasan tablet ACTOS
Tablet Actos 15 mg berwarna putih bulat ditandai dengan tulisan ‘15’ pada salah satu sisinya, dan mengandung piaglitazone 15 mg pada setiap tabletnya.

Tablet Actos 30 mg berwarna putih bulat ditandai dengan tulisan ‘’30’’ pada salah satu sisinya, dan mengandung piaglitazone 30 mg pada setiap tabletnya

Tablet ACTOS 15 mg dikemas dengan kemasan box berisi 2 blister dan berisi 7 tablet pada tiap-tiap blisternya.

Tablet ACTOS 30 mg dikemas dengan kemasan box berisi 2 blister dan berisi 7 tablet pada tiap-tiap blisternya.

Produk ini dipasarkan di Indonesia oleh pemegang izin edar,

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