20000XXXX

GLIT 15 / GLIT 30

Pioglitazone Tablets 15mg & 30mg

COMPOSITION:

GLIT 15 (Pioglitazone Tablets 15mg)

Each uncoated tablet contains

Pioglitazone Hydrochloride equivalent to Pioglitazone	15mg
Excipients	q.s.

GLIT 30 (Pioglitazone Tablets 30mg)

Each uncoated tablet contains

Pioglitazone Hydrochloride equivalent to Pioglitazone	30mg
Excipients	q.s.

PRESENTATION:

GLIT 15 (Pioglitazone Tablets 15mg) - White to off white, round, biconvex, uncoated tablets embossed "15" on one side and plain on other side.

GLIT 30 (Pioglitazone Tablets 30mg) - White to off white, round, flat, beveled edged, uncoated tablets embossed "30" on one side and plain on the other side.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS:

Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins; ATC code: A10BG03.

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

Fasting and postprandial glycaemic control is improved in patients with type 2 diabetes mellitus. The improved glycaemic control is associated with a reduction in both fasting and postprandial plasma insulin concentrations.

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. Reduced total plasma triglycerides and free fatty acids, and increased HDL-cholesterol levels were observed with small, but not clinically significant increases in LDL-cholesterol levels.

Pioglitazone reduced total plasma triglycerides and free fatty acids, and increased HDL cholesterol levels, compared with metformin or gliclazide. Pioglitazone did not cause significant increases in LDL cholesterol levels, whilst reductions were observed with metformin and gliclazide. 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 significantly different to glibenclamide.

PHARMACOKINETICS AND DRUG METABOLISM

Absorption

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

Distribution

The estimated volume of distribution in humans is 0.25 l/kg.

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

Biotransformation

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

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

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

Elimination

Following oral administration of radio labelled pioglitazone, recovered label was mainly in faeces (55%) and a lesser amount in urine (45%). The mean plasma elimination half-life of unchanged pioglitazone in man is 5 to 6 hours and for its total active metabolites 16 to 23 hours.

Elderly

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

Patients with renal impairment

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

Patients with hepatic impairment

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

INDICATIONS AND USAGE

GLIT is indicated as oral monotherapy in type 2 diabetes mellitus patients, particularly overweight patients, inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance.

GLIT is also indicated for oral combination treatment in type 2 diabetes mellitus patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or sulphonylurea:

- In combination with metformin particularly in overweight patients
- In combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated

DOSAGE AND ADMINISTRATION

GLIT should be taken orally once daily with or without food.

Dosage in Adults

GLIT may be initiated at 15 mg or 30mg once daily. The dose may be increased in increments up to 45mg once daily.

In combination with metformin, the current metformin dose can be continued upon initiation of pioglitazone therapy.

In combination with sulphonylurea, the current sulphonylurea dose can be continued upon initiation of pioglitazone therapy. If patients report hypoglycaemia, the dose of sulphonylurea 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 > 4ml/min). No information is available from dialysed patients therefore pioglitazone should not be used in such patients.

Patients with hepatic impairment

GLIT should not be used in patients with hepatic impairment.

Children and adolescents

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

CONTRAINDICATIONS

Pioglitazone is contraindicated in patients with:

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluid retention and cardiac failure

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

Elderly

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

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

Bladder cancer

Cases of bladder cancer were reported more frequently. 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.

Monitoring of liver function

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

Following initiation of therapy with pioglitazone, it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3

Size: 200mm x 400 mm

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

Weight gain

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

Haematology

There was a small reduction in mean haemoglobin and haematocrit reported during therapy with pioglitazone, consistent with haemodilution. Similar changes were seen in metformin and to a lesser extent sulphonylurea and insulin treated patients compared with pioglitazone.

Hypoglycaemia

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

Eye disorders

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

Others

An increased incidence in bone fractures in women was seen on treatment for up to 3.5 years. No increase in fracture rates was observed in men treated with pioglitazone.

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, pioglitazone treatment in patients with polycystic ovarian syndrome may result in resumption of ovulation. These patients may be at risk of pregnancy. Patients should be aware of the risk of pregnancy and if a patient wishes to become pregnant or if pregnancy occurs, the treatment should be discontinued.

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.

Pioglitazone tablets contain lactose monohydrate and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

DRUG INTERACTIONS

Pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Co-administration of pioglitazone with sulphonylureas does not appear to affect the pharmacokinetics of the sulphonylurea. No induction of the main inducible cytochrome P450, 1A, 2C8/9 and 3A4. No inhibition of any subtype of cytochrome P450. Interactions with substances metabolised by these enzymes, e.g. oral contraceptives, cyclosporin, calcium channel blockers, and HMGCoA reductase inhibitors are not to be expected.

Co-administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) has been reported to result in a 3-fold increase in AUC of pioglitazone. Since there is a potential for an increase in dose-related adverse events, a decrease in the dose of pioglitazone may be needed when gemfibrozil is concomitantly administered. Close monitoring of glycaemic control should be considered. Co-administration of pioglitazone with rifampicin (an inducer of cytochrome P450 2C8) reported to result in a decrease in AUC of pioglitazone. The pioglitazone dose may need to be increased when rifampicin is concomitantly administered. Close monitoring of glycaemic control should be considered.

PREGNANCY AND LACTATION

Pregnancy

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

Breast-feeding

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

Fertility

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

SIDE EFFECTS

Frequencies are defined as: very common; common; uncommon; rare; very rare; not known. Within each system organ class, adverse reactions are presented in order of decreasing incidence followed by decreasing seriousness.

Adverse reaction	Frequency of adverse reactions of Pioglitazone by treatment regimen				
	Monotherapy	Combination			
		with metformin	with sulphonylurea	with metformin and sulphonylurea	with insulin
Infections and infestations					
upper respiratory tract infection	common	common	common	common	common
bronchitis					common
sinusitis	uncommon	uncommon	uncommon	uncommon	uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)					
bladder cancer	uncommon	uncommon	uncommon	uncommon	uncommon
Blood and lymphatic system disorders					
anaemia		common			
Immune System Disorders					
hypersensitivity and allergic reactions	not known	not known	not known	not known	not known
Metabolism and nutrition disorders					
hypo-glycaemia			uncommon	very common	common
appetite increased			uncommon		
Nervous system disorders					
hypo-aesthesia	common	common	common	common	common
headache		common	uncommon		
dizziness			common		
insomnia	uncommon	uncommon	uncommon	uncommon	uncommon
Eye disorders					
visual disturbance	common	common	uncommon		
macular oedema	not known	not known	not known	not known	not known
Ear and labyrinth disorders					
vertigo			uncommon		
Cardiac disorders					
heart failure					common
Respiratory, thoracic and mediastinal disorders					
dyspnoea					common
Gastrointestinal disorders					
flatulence		uncommon	common		
Skin and subcutaneous tissue disorders					
sweating			uncommon		
Musculoskeletal and connective tissue disorders					
fracture bone	common	common	common	common	common
arthralgia		common		common	common
back pain					common
Renal and urinary disorders					
haematuria		common			
glycosuria			uncommon		
proteinuria			uncommon		
Reproductive system and breast disorders					
erectile dysfunction		common			
General disorders and administration site conditions					
Oedema					very common
fatigue			uncommon		
Investigations					
weight increased	common	common	common	common	common
blood creatine phospho-kinase increased				common	
increased lactic dehydro-genase			uncommon		
alanine aminotransferase increased	not known	not known	not known	not known	not known

OVERDOSAGE

The maximum reported dose of 120 mg/day for four days, then 180 mg/day for seven days was not associated with any symptoms. Hypoglycaemia may occur in combination with sulphonylureas or insulin. Symptomatic and general supportive measures should be taken in case of overdose.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

Pioglitazone 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.

INSTRUCTIONS FOR USE

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

STORAGE CONDITION

Store below 30°C. Protect from light & moisture.

PACK SIZE

28's Tablets

Alu/ Alu Cold form Laminate with Printed aluminium foil blister of 14 tablets. Such 2 blisters of 14 tablets each are packed in a carton along with insert.

PRODUCT REGISTRATION HOLDER

Synerrv Sdn Bhd, S0-29-2, Menara 1, KL Eco City, Jalan Bangsar, KG Haji Abdullah, Hukum, 59200 Kuala Lumpur Malaysia

MANUFACTURER

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