PIOGLITAZONE HCl + GLIMEPIRIDE

3012725

ASENZA PLUS®

15mg / 1mg Tablet
15mg / 2mg Tablet
30mg / 2mg Tablet
45mg / 2mg Tablet
15mg / 4mg Tablet
30mg / 4mg Tablet
45mg / 4mg Tablet
ANTI-DIABETIC

FORMULATION

Each uncoated tablet contains :

Pioglitazone (as hydrochloride)	15mg
Glimepiride USP	1mg
Pioglitazone (as hydrochloride)	15mg
Glimepiride USP	2mg
Pioglitazone (as hydrochloride)	30mg
Glimepiride USP	2mg
Pioglitazone (as hydrochloride)	45mg
Glimepiride USP	2mg
Pioglitazone (as hydrochloride)	15mg
Glimepiride USP	4mg
Pioglitazone (as hydrochloride)	30mg
Glimepiride USP	4mg
Pioglitazone (as hydrochloride)	45mg
Glimepiride USP	4mg

DESCRIPTION

15mg/2mg-White to off white colored, circular, flat, beveled edged, uncoated tablets, plain on both sides.
30mg/2mg-White to off white colored, circular, flat, beveled edged, uncoated tablets with break line on one side.

MECHANISM OF ACTION

Asenza Plus combines two antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: Pioglitazone hydrochloride, a member of the thiazolidinedione class, and Glimepiride, a member of the sulfonylurea class. Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas sulfonylureas are insulin secretogogues that act primarily by stimulating release of insulin from functioning pancreatic beta cells.

Pioglitazone HCl : Pioglitazone depends on the presence of insulin for its mechanism of action. Pioglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important 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 control of glucose and lipid metabolism.

In animal models of diabetes, Pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by Pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.

Since Pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Glimepiride: The primary mechanism of action of Glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of sulfonylureas such as Glimepiride. This is supported by both preclinical and clinical studies demonstrating that Glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These findings are consistent with the results of a long-term, randomized, placebo-controlled trial in which Glimepiride therapy improved postprandial insulin/C-peptide responses and overall glycemic control without producing clinically meaningful increases in fasting insulin/C-peptide levels. However, as with other sulfonylureas, the mechanism by which Glimepiride lowers blood glucose during long-term administration has not been clearly established.

PHARMACOKINETICS

Pioglitazone HCl is rapidly absorbed after oral administration. Peak plasma concentrations are obtained within 2 hours and bioavailability exceeds 80%. Pioglitazone is more than 99% bound to plasma proteins. It is extensively metabolized by cytochrome P450 isoenzymes CYP3A4 and CYP2C9 to both active and inactive metabolites. It is excreted in the urine and feces and has a plasma half-life of up to 7 hours. The active metabolites have a half-life of up to 24 hours.

Absorption:

Pioglitazone HCl

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.

Glimepiride

After oral administration, Glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with type 2 diabetes have shown significant absorption of Glimepiride within 1 hour after administration and C_{max} at 2 to 3 hours. When Glimepiride was given with meals, the mean Tmax was slightly increased (12%) and the mean C_{max} and the total area under the serum concentration-time curve (AUC) were slightly decreased (8% and 9%, respectively).

Distribution:

Pioglitazone HCl

The mean apparent volume of distribution (Vd/F) of Pioglitazone following single-dose administration is 0.63±0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%) in human serum, principally to serum albumin. Pioglitazone also binds to their serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (>98%) to serum albumin.

Glimepiride

After intravenous (IV) dosing in normal subjects, Vd/F was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metabolism:

Pioglitazone HCl

Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate 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 drug-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.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of Pioglitazone. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1. In vivo studies of Pioglitazone in combination with P450 inhibitors and substrates have been performed. Urinary 6β-hydroxycortisol/cortisol ratios measured in patients treated with Pioglitazone showed that Pioglitazone is not a strong CYP3A4 enzyme inducer.

Glimepiride

Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). CYP2C9 has been shown to be involved in the biotransformation of Glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1 is clinically meaningful is not clear.

Excretion and Elimination:

Pioglitazone HCl

Following oral administration, approximately 15% to 30% of the Pioglitazone dose is recovered in the urine. Renal elimination of Pioglitazone is negligible and the drug 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 feces.

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.

Glimepiride

When C-glimepriride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent drug was recovered from urine or feces. After IV dosing in patients, no significant biliary excretion of Glimepiride or its M1 metabolite has been observed.

INDICATIONS

Pioglitazone plus Glimepiride tablet is indicated as an adjunct to diet and exercise as a once-daily combination therapy to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of Pioglitazone and a sulfonylurea urea or whose diabetes is not adequately controlled with a sulfonylurea alone, or for those patients who have initially responded to Pioglitazone alone and require additional glycemic control.

Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise. These efforts are important not only in the primary treatment of type 2 diabetes, but also to maintain the efficacy of drug therapy.

CONTRAINDICATIONS

Pioglitazone hydrochloride and Glimepiride tablet is contraindicated in patients with: known hypersensitivity to Pioglitazone, Glimepiride or any other component of Pioglitazone plus Glimepiride tablet; diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

DOSAGE AND ADMINISTRATION

General

The use of antihyperglycemic therapy in the management of type 2 diabetes should be individualized on the basis of effectiveness and tolerability. Failure to follow an appropriate dosage regimen may precipitate hypoglycemia.

Dosage Recommendations

Selecting the starting dose of Pioglitazone plus Glimepiride tablet should be based on the patient's current regimen of Pioglitazone and/or sulfonylurea. Those patients who may be more sensitive to antihyperglycemic drugs should be monitored carefully during dose adjustment. It is recommended that a single dose of Pioglitazone plus Glimepiride tablet be administered once daily with the first main meal.

Starting dose for patients currently on Glimepiride monotherapy

Based on the usual starting dose of Pioglitazone (15 mg or 30 mg daily), Pioglitazone plus Glimepiride tablet may be initiated at 30 mg/2 mg or 30 mg/4mg tablet strengths once daily, and adjusted after assessing adequacy of therapeutic response. Or as prescribed by the physician.

For patients with type 2 diabetes and systolic dysfunction, see **DOSAGE AND ADMINISTRATION, Special Patient Populations.**

Starting dose for patients currently on Pioglitazone monotherapy

Based on the usual starting doses of Glimepiride (1 mg or 2 mg once daily), and Pioglitazone 15 mg or 30 mg. Pioglitazone plus Glimepiride tablet may be initiated at 30 mg/2 mg once daily, and adjusted after assessing adequacy of therapeutic response.

For patients who are not currently on Glimepiride and may be more sensitive to hypoglycemia, see **DOSAGE AND ADMINISTRATION,**

Starting dose for patients switching from combination therapy of Pioglitazone plus Glimepride as separate tablets

Pioglitazone plus Glimepiride tablet may be initiated with 30 mg/2mg or 30 mg /4 mg tablet strengths based on the dose of Pioglitazone and Glimepiride already being taken. Patients who are not controlled with 15 mg of Pioglitazone in combination with Glimepiride should be carefully monitored when switched to Pioglitazone plus Glimepiride tablet.

Starting dose for patients currently on a different sulfonylurea monotherapy or switching from combination therapy of Pioglitazone plus a different sulfonylurea (e.g. glyburide, glipizide, chlorpropamide, tolbutamide, acetohexamide)

No exact dosage relationship exists between Glimepiride and the other sulfonylurea agents. Therefore, based on the maximum starting dose of 2 mg Glimepiride, Pioglitazone plus Glimepiride tablet should be limited initially to a starting dose of 30 mg/2mg once daily, and adjusted after assessing adequacy of therapeutic response.

Any change in diabetic therapy should be undertaken with care and appropriate monitoring as changes in glycemic control can occur. Patients should be observed carefully for hypoglycemia (1-2 weeks) when being transferred to Pioglitazone plus Glimepiride tablet, especially from longer half-life sulfonylureas (e.g. chlorpropamide) due to potential overlapping of drug effect.

Sufficient time should be given to assess adequacy of therapeutic response. Ideally, the response to therapy should be evaluated using A1C, which is better indicator of long-term glycemic control than FPG alone. A1C reflects glycemia over the past two to three months. In clinical use, it is recommended that patients be treated with Pioglitazone plus Glimepiride tablet for a period of time adequate to evaluate change in A1C (8-12 weeks) unless glycemic control as measured by FPG deteriorates.

Special Patient Populations

Pioglitazone plus Glimepiride tablet is not recommended for use in pregnancy, nursing mothers or for use in pediatric patients.

In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage of Pioglitazone plus Glimepiride tablet should be conservative to avoid hypoglycemic reactions. These patients should be started at 1 mg Glimepiride prior to prescribing Pioglitazone plus Glimepiride tablet. During initiation of Pioglitazone plus Glimepiride tablet therapy and any subsequent dose adjustment, patients should be observed carefully for hypoglycemia.

Therapy with Pioglitazone plus Glimepiride tablet should not 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 plus Glimepiride tablet and periodically thereafter.

The lowest approved dose of Pioglitazone plus Glimepiride tablet therapy should be prescribed to patients with type 2 diabetes and systolic dysfunction only after titration from 15 mg to 30 mg of Pioglitazone has been safely tolerated. If subsequent dose adjustment is necessary, patients should be carefully monitored for weight gain, edema, or signs and symptoms of CHF exacerbation.

Maximum Recommended Dose

Pioglitazone plus Glimepiride tablet are available as a 15 mg Pioglitazone plus 2 mg Glimepiride or a 30 mg Pioglitazone plus 2 mg Glimepiride or a 30 mg Pioglitazone plus 4 mg Glimepiride formulation for oral administration. The maximum recommended daily dose for Pioglitazone is 45 mg and the maximum recommended daily dose for Glimepiride is 8 mg.

Pioglitazone plus Glimepiride tablet should therefore not be given more than once daily at any of the tablet strengths.

PRECAUTIONS

General: Pioglitazone HCl

Pioglitazone exerts its antihyperglycemic effect only in the presence of insulin. Therefore, Pioglitazone plus Glimepiride tablet should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia: patients receiving Pioglitazone in

combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Cardiovascular: In U.S. placebo-controlled clinical trials that excluded patients with New York Heart Association (NYHA) Class III and IV cardiac status, the incidence of serious cardiac adverse events related to volume expansion was not increased in patients treated with Pioglitazone as monotherapy or in combination with sulfonylureas or metformin vs. placebo-treated patients. In insulin combination studies, a small number of patients with a history of previously existing cardiac developed congestive heart failure when treated with Pioglitazone in combination with insulin. Patients with NYHA Class III and IV cardiac status were not studied in pre-approval Pioglitazone clinical trials. Pioglitazone is not indicated in patients with NYHA Class III or IV cardiac status.

In post marketing experience with Pioglitazone, cases of congestive heart failure have been reported in patients both with and without previously known heart disease.

Edema: In all U.S. clinical trials with Pioglitazone, edema was reported more frequently in patients treated with Pioglitazone than in placebo-treated with Pioglitazone than in placebo-controlled and appears to be dose related. In post marketing experience, reports of initiation or worsening of edema have been received. Pioglitazone plus Glimepiride tablet should be used with caution in patients with edema.

Weight Gain: Dose related weight gain was observed with Pioglitazone alone in combination with other hypoglycemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Ovulation: Therapy with Pioglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. Thus, adequate contraception in premenopausal women should be recommended while taking Pioglitazone plus Glimepiride tablet. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Hematologic: Across all clinical studies with Pioglitazone, mean hemoglobin values declined by 2% to 4% in patients treated with Pioglitazone. These changes primarily occurred within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume and have rarely been associated with any significant hematologic clinical effects. Pioglitazone plus Glimepiride tablet may cause decreases in hemoglobin and hematocrit.

Hepatic Effects: In There was no evidence of drug-induced hepatotoxicity or elevation of LAT levels in the clinical studies.

General: Glimepiride

Hypoglycemia: All sulfonylurea are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of Glimepiride. A starting dose of 1 mg of Glimepiride once daily followed by appropriate dose titration is recommended in those patients. Debilitated or malnourished patients and those with adrenal, pituitary, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used. Combined use of Glimepiride with insulin or metformin may increase the potential for hypoglycemia.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. The effectiveness of any oral hypoglycemic drug, including Pioglitazone plus Glimepiride tablet, in lowering blood glucose to a desired level decreases in many patient over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug.

Use during Pregnancy and Lactation

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. Pioglitazone plus Glimepiride tablet should not be used during pregnancy unless the potential benefits justify the potential risk to the fetus.

There are no adequate and well-controlled studies in pregnant women with Pioglitazone plus Glimepiride tablet or its individual components. No animal studies have been conducted with the combined products in Pioglitazone plus Glimepiride tablet. The following data are based on findings in studies performed with Pioglitazone and Glimepiride individually.

Use in Pediatric

Safety and effectiveness of Pioglitazone plus Glimepiride tablet in pediatric patients have not been established.

Use in Elderly

Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs. In elderly, debilitated, or malnourished patients, or in patients with renal and hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative based upon blood glucose levels prior to and after initiation of treatment to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents.

DRUG INTERACTIONS

Pioglitazone HCl

In vivo drug-drug interaction studies have suggested that Pioglitazone may be weak inducer of CYP 450 isoform 3A4 substrate.

An enzyme inhibitor of CYP2C8 (such as gemfibrozil) may significantly increase the AUC of Pioglitazone and an enzyme inducer of CYP2C8 (such as rifampin) may significantly decrease the AUC of Pioglitazone. Therefore, if an inhibitor or inducer of CYP2C8 is started or stopped during treatment with Pioglitazone, changes in diabetes treatment may be needed based on clinical response.

Glimepiride

A diminished hypoglycemic effect, possibly requiring an increased dose of Glimepiride, has been seen or might be expected on theoretical grounds with adrenaline (epinephrine), aminoglutethimide, chlorpromazine, corticosteroids, diazoxide, oral contraceptives, rifamycins and thiazides diuretics.

An increased hypoglycemic effect has occurred or might be expected with ACE inhibitors, alcohol, allopurinol, some analgesics (notably azapropazone, phenylbutazone and the salicylates), azole antifungals (fluconazole, ketoconazole and miconazole), chloramphenicol, cimetidine, clofibrate and related compounds, coumarin anticoagulants, halofenate, heparin, MAOIs, octreotide (although this may also produce hyperglycemia), ranitidine, sulfinpyrazone, sulfonamides (including co-trimoxazole), tetracyclines, tricyclic antidepressants and thyroid hormones.

Beta blockers have been reported both to increase hypoglycemia and to mask typical sympathetic warning signs. There are sporadic and conflicting reports of a possible interaction with calcium channel blocker, but overall any effect seems to be of little clinical significance.

In addition to producing hypoglycemia alcohol can interact with chlorpropamide to produce an unpleasant flushing reaction. Such an effect is rare with other sulfonylureas and alcohol.

ADVERSE EFFECTS

Pioglitazone HCl

Most clinical adverse events were similar between groups treated with Pioglitazone in combination with a sulfonylurea and those treated with Pioglitazone monotherapy. Other adverse events reported in at least 5 % of patients in controlled clinical studies between placebo and Pioglitazone monotherapy included myalgia (2.7% and 5.4%), tooth disorder (2.3% and 5.3%), diabetes mellitus aggravated (8.1% and 5.1%), and pharyngitis (0.8% and 5.1%), respectively.

In monotherapy studies, edema was reported for 4.8% (with doses from 7.5 mg to 45 mg) of patients treated with Pioglitazone versus 1.2% of placebo-treated patients. Most of these events were considered mild or moderate in intensity (see PRECAUTIONS, General: Pioglitazone hydrochloride, Edema).

Postmarketing reports of new onset or worsening diabetic macular edema with decreased visual acuity have also been received (see PRECAUTIONS, General: Pioglitazone hydrochloride).

The drug should not be used as first line of therapy for diabetes.

Advice for healthcare professionals:

- **Patients with active bladder cancer or with a history of bladder cancer, and those with uninvestigated haematuria, should not receive pioglitazone**
- **Prescribers should review the safety and efficacy of pioglitazone in individuals after 3-6 months of treatment to ensure that only patients who are deriving benefit continue to be treated. Pioglitazone should be stopped in patients who do not respond adequately to treatment (eg. reduction in glycosylated hemoglobin HbA1c)**
- **Before starting pioglitazone, the following known risk factors for development of bladder cancer should be assessed in individuals: age, current or past history of smoking, exposure to some occupational or chemotherapy agents such as cyclophosphamide, or previous irradiation of the pelvic region**
- **Use in elderly patients should be considered carefully before and during treatment because the risk of bladder cancer increases with age. Elderly patients should start on the lowest possible dose and be regularly monitored because of the risks of bladder cancer and heart failure associated with pioglitazone.**

Glimepiride

Adverse events that occurred in controlled clinical trials with placebo and Glimepiride monotherapy, other than hypoglycemia, headache and nausea, also included dizziness (0.3% and 1.7%) and asthenia (1.0% and 1.6%), respectively.

Gastrointestinal Reactions: Vomiting, gastrointestinal pain, and diarrhea have been reported with Glimepiride, but the incidence in placebo-controlled trials was less than 1%. In rare cases, there may be an elevation of liver enzyme levels. In isolated instances, impairment of liver function (e.g. with cholestasis and jaundice), as well as hepatitis, which may also lead to liver failure have been reported with sulfonylureas, including Glimepiride.

Dermatologic Reactions: Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of Glimepiride-treated patients. These may be transient and may disappear despite continued use of Glimepiride. If those hypersensitivity reactions persist or worsen, the drug should be discontinued. Porphyria cutanea tarda, photosensitivity reactions, and allergic vasculitis have been reported with sulfonylureas.

Metabolic Reactions: hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas; however, no cases have yet been reported with Glimepiride tablets. Cases of hyponatremia have been reported with Glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylyreas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Other Reactions: Changes in accommodation and/or blurred vision may occur with the use of Glimepiride. In placebo-controlled trials of Glimepiride, the incidence of blurred vision with placebo was 0.7% and with Glimepiride, 0.4%. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment.

OVERDOSAGE, SYMPTOMS AND ANTIDOTE

Pioglitazone HCl

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

Glimepiride

Overdosage of sulfonylureas, including Glimepiride, can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

STORE AT TEMPERATURES NOT EXCEEDING 30° C.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA : www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

AVAILABILITY

Pioglitazone HCl 15mg + Glimepiride 1mg (ASENZA PLUS®) Tablet X Alu / PVC blister pack of 10's, box of 30 tablets

Pioglitazone HCl 15mg + Glimepiride 2mg (ASENZA PLUS®) Tablet X Alu / PVC blister pack of 10's, box of 30 tablets

Pioglitazone HCl 30mg + Glimepiride 2mg (ASENZA PLUS®) Tablet X Alu / PVC blister pack of 10's, box of 30 tablets

Pioglitazone HCl 45mg + Glimepiride 2mg (ASENZA PLUS®) Tablet X Alu / PVC blister pack of 10's, box of 30 tablets

Pioglitazone HCl 15mg + Glimepiride 4mg (ASENZA PLUS®) Tablet X Alu / PVC blister pack of 10's, box of 30 tablets

Pioglitazone HCl 30mg + Glimepiride 4mg (ASENZA PLUS®) Tablet X Alu / PVC blister pack of 10's, box of 30 tablets

Pioglitazone HCl 45mg + Glimepiride 4mg (ASENZA PLUS®) Tablet X Alu / PVC blister pack of 10's, box of 30 tablets

ASENZA PLUS® is a registered trademark of Ajanta Pharma Philippines, Inc.

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