For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

AZULIX

Glimepiride 1mg, 2mg, 3mg and 4mg Tablets

COMPOSITION

AZULIX-1
Each uncoated tablet contains:
Glimepiride I.P. 1mg
Colour: Red oxide of Iron

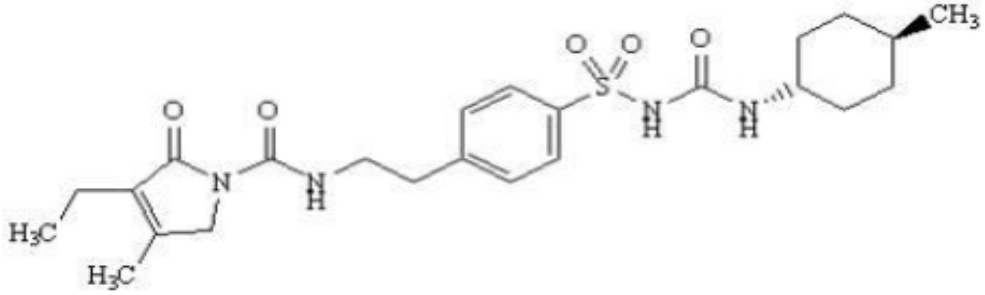
AZULIX-2
Each uncoated tablet contains:
Glimepiride I.P. 2mg
Colour: Yellow oxide of Iron

AZULIX-3
Each uncoated tablet contains:
Glimepiride I.P. 3mg

AZULIX-4
Each uncoated tablet contains:
Glimepiride I.P. 4mg
Colour: Lake of quinoline yellow

DESCRIPTION

Glimepiride is an oral blood-glucose-lowering drug of the sulfonylurea class. Glimepiride is a white to yellowish-white, crystalline, odorless to practically odorless powder. Chemically, glimepiride is identified as 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea.
It had a molecular formula of $C_{24}H_{34}N_4O_5S$ and a molecular weight of 490.62.
The structural formula is:



CLINICAL PHARMACOLOGY

Mechanism of Action
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/Cpeptide 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.

Glimepiride is effective as initial drug therapy. In patients where monotherapy with glimepiride or metformin has not produced adequate glycemic control, the combination of glimepiride and metformin may have a synergistic effect, since both agents act to improve glucose tolerance by different primary mechanisms of action. This complementary effect has been observed with metformin and other sulfonylureas, in multiple studies.

Pharmacodynamics

A mild glucose lowering effect appeared at dose as low as 0.5-0.6mg in healthy subjects reported and time required to reach the maximum effects (i.e., minimum blood glucose level [T_{min}]) was 2 to 3 hours. In noninsulin-dependent (Type 2) diabetes mellitus (NIDDM) patients, both fasting and 2-hour postprandial glucose levels were significantly lower with glimepiride (1, 2, 4, and 8 mg once daily) than with placebo after 14 days of oral dosing. The glucose-lowering effect in all active treatment groups was maintained over 24 hours.

In larger dose-ranging studies, blood glucose and HbA1c were found to respond in a dose-dependent manner over the range of 1 to 4 mg/day of glimepiride. Some patients, particularly those with higher fasting plasma glucose (FPG) levels, may benefit from doses of glimepiride up to 8 mg once daily. No difference in response was reported when glimepiride was administered once or twice daily.

In two 14-week, placebo-controlled studies in 720 subjects, the average net reduction in HbA1c for glimepiride tablets patients treated with 8 mg once daily was 2.0% in absolute units compared with placebo-treated patients. In a long-term, randomized, placebocontrolled study of Type 2 diabetic patients unresponsive to dietary management, glimepiride therapy improved postprandial insulin/C-peptide responses, and 75% of patients achieved and maintained control of blood glucose and HbA1c. Efficacy results were not affected by age, gender, weight, or race.

In long-term extension trials with previously-treated patients, no meaningful deterioration in mean fasting blood glucose (FBG) or HbA1c levels was reported after 2 1/2 years of glimepiride therapy.

It was reported that combination therapy with glimepiride and insulin (70% NPH/30% regular) was compared to placebo/insulin in secondary failure patients whose body

weight was >130% of their ideal body weight. Initially, 5–10 units of insulin were administered with the main evening meal and titrated upward weekly to achieve predefined FPG values. Both groups in this double-blind study achieved similar reductions in FPG levels but the glimepiride /insulin therapy group used approximately 38% less insulin.

Glimepiride therapy is effective in controlling blood glucose without deleterious changes in the plasma lipoprotein profiles of patients treated for Type 2 diabetes.

Pharmacokinetic

Absorption:

Studies with single oral doses of glimepiride in healthy subjects and with multiple oral doses in patients with type 2 diabetes showed peak drug concentrations (Cmax) 2 to 3 hours post-dose. When glimepiride was given with meals, the mean Cmax and AUC (area under the curve) were decreased by 8% and 9%, respectively.

Glimepiride does not accumulate in serum following multiple dosing. The pharmacokinetics of glimepiride does not differ between healthy subjects and patients with type 2 diabetes. Clearance of glimepiride after oral administration does not change over the 1 mg to 8 mg dose range, indicating linear pharmacokinetics. In healthy subjects, the intra- and inter-individual variabilities of glimepiride pharmacokinetic parameters were 15-23% and 24-29%, respectively.

Distribution:

After intravenous dosing in healthy subjects, the volume of distribution (Vd) 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:

Glimepiride is completely metabolized by oxidative biotransformation after either an intravenous or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 is involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M2 is inactive. In animals, M1 possesses about one-third of the pharmacological activity of glimepiride, but it is unclear whether M1 results in clinically meaningful effects on blood glucose in humans.

Excretion:

When ^{14}C-glimepiride was given orally to 3 healthy male subjects, approximately 60% of the total radioactivity was recovered in the urine in 7 days. M1 and M2 accounted for 80-90% of the radioactivity recovered in the urine. The ratio of M1 to M2 in the urine was approximately 3:2 in two subjects and 4:1 in one subject. Approximately 40% of the total radioactivity was recovered in feces. M1 and M2 accounted for about 70% (ratio of M1 to M2 was 1:3) of the radioactivity recovered in feces. No parent drug was recovered from urine or feces. After intravenous dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite was observed.

Geriatric Patients:
A comparison of glimepiride pharmacokinetics in patients with type 2 diabetes ≤65 years and those >65 years was evaluated in a multiple-dose study using Glimepiride 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean AUC at steady state for the older patients was approximately 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was approximately 11% higher than that for the younger patients.

Gender:
There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight.

Race:
No studies have been conducted to assess the effects of race on glimepiride pharmacokinetics but in placebo-controlled trials of Glimepiride in patients with type 2 diabetes, the reduction in HbA_{1C} was comparable in Caucasians (n = 536), blacks (n = 63), and Hispanics (n = 63).

Renal Impairment:
A single-dose, open-label study Glimepiride 3 mg was administered to patients with mild, moderate and severe renal impairment as estimated by creatinine clearance (CLcr): Group I consisted of 5 patients with mild renal impairment (CLcr > 50 mL/min), Group II consisted of 3 patients with moderate renal impairment (CLcr = 20-50 mL/min) and Group III consisted of 7 patients with severe renal impairment (CLcr < 20 mL/min). Although, glimepiride serum concentrations decreased with decreasing renal function, Group III had a 2.3-fold higher mean AUC for M1 and an 8.6-fold higher mean AUC for M2 compared to corresponding mean AUCs in Group I. The apparent terminal half-life (T1/2) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as a percentage of dose decreased from 44.4% for Group I to 21.9% for Group II and 9.3% for Group III.

Hepatic Impairment:
It is unknown whether there is an effect of hepatic impairment on Glimepiride pharmacokinetics because the pharmacokinetics of Glimepiride has not been adequately evaluated in patients with hepatic impairment.

Obese Patients:
The pharmacokinetics of glimepiride and its metabolites were measured in a single-dose study involving 28 patients with type 2 diabetes who either had normal body weight or were morbidly obese. While the tmax, clearance, and volume of distribution of glimepiride in the morbidly obese patients were similar to those in the normal weight group, the morbidly obese had lower Cmax and AUC than those of normal body weight. The mean Cmax, AUC0-24, AUC0-∞ values of glimepiride in normal vs. morbidly obese patients were 547 ± 218 ng/mL vs. 410 ± 124 ng/mL, 3210 ± 1030 hours·ng/mL vs. 2820 ± 1110 hours·ng/mL and 4000 ± 1320 hours·ng/mL vs. 3280 ± 1360 hours·ng/mL, respectively.

INDICATIONS

Azulix is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with non-insulin dependant (type-II) diabetes mellitus whose hyperglycemia cannot be controlled by diet and exercise alone.

DOSAGES AND ADMINISTRATION

Glimepiride should be administered with breakfast or the first main meal of the day. The recommended starting dose of Glimepiride is 1 mg or 2 mg once daily. Patients at increased risk for hypoglycemia (e.g., the elderly or patients with renal impairment) should be started on 1 mg once daily.

After reaching a daily dose of 2 mg, further dose increases can be made in increments of 1 mg or 2 mg based upon the patient's glycemic response. Uptitration should not occur more frequently than every 1-2 weeks. A conservative titration scheme is recommended for patients at increased risk for hypoglycemia. The maximum recommended dose is 8 mg once daily.

Patients being transferred to Glimepiride from longer half-life sulfonylureas (e.g., chlorpropamide) may have overlapping drug effect for 1-2 weeks and should be appropriately monitored for hypoglycemia.

When colesevelam is coadministered with glimepiride, maximum plasma concentration and total exposure to glimepiride is reduced. Therefore, Glimepiride should be administered at least 4 hours prior to colesevelam.

CONTRAINDICATION

Glimepiride is contraindicated in patients with a history of a hypersensitivity reaction to:

• Glimepiride or any of the product's ingredients.

Sulfonamide derivatives: Patients who have developed an allergic reaction to sulfonamide derivatives may develop an allergic reaction to Glimepiride. Do not use Glimepiride in patients who have a history of an allergic reaction to sulfonamide derivatives.

Reported hypersensitivity reactions include cutaneous eruptions with or without pruritus as well as more serious reactions (e.g. anaphylaxis, angioedema, Stevens-Johnson syndrome, dyspnea)

WARNINGS AND PRECAUTIONS

Hypoglycemia

All sulfonylureas, including Glimepiride can cause severe hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. These impairments may present a risk in situations where these abilities are especially

important, such as driving or operating other machinery. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death.

Patients must be educated to recognize and manage hypoglycemia. Use caution when initiating and increasing Glimepiride doses in patients who may be predisposed to hypoglycemia (e.g., the elderly, patients with renal impairment, and patients on other anti-diabetic medications). Debilitated or malnourished patients and those with adrenal, pituitary, or hepatic impairment are particularly susceptible to the hypoglycemic action of glucose-lowering medications. Hypoglycemia is also more likely to occur when caloric intake is deficient, after severe or prolonged exercise, or when alcohol is ingested.

Early warning symptoms of hypoglycemia may be different or less pronounced in patients with autonomic neuropathy, the elderly, and in patients who are taking beta-adrenergic blocking medications or other sympatholytic agents. These situations may result in severe hypoglycemia before the patient is aware of the hypoglycemia.

Hypersensitivity Reactions
There have been postmarketing reports of hypersensitivity reactions in patients treated with Glimepiride, including serious reactions such as anaphylaxis, angioedema, and Stevens-Johnson Syndrome. If a hypersensitivity reaction is suspected, promptly discontinue Glimepiride, assess for other potential causes for the reaction, and institute alternative treatment for diabetes.

Hemolytic Anemia
Sulfonylureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because Glimepiride is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative. There are also postmarketing reports of hemolytic anemia in patients receiving Glimepiride who did not have known G6PD deficiency.

Increased Risk of Cardiovascular Mortality with Sulfonylureas
The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase

in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of Glimepiride and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Glimepiride or any other anti-diabetic drug.

DRUG INTERACTIONS
Drugs Affecting Glucose Metabolism
A number of medications affect glucose metabolism and may require Glimepiride dose adjustment and particularly close monitoring for hypoglycemia or worsening glycemic control.

The following are examples of medications that may increase the glucose-lowering effect of sulfonylureas including Glimepiride, increasing the susceptibility to and/or intensity of hypoglycemia: oral anti-diabetic medications, pramlintide acetate, insulin, angiotensin converting enzyme (ACE) inhibitors, H2 receptor antagonists, fibrates, propoxyphene, pentoxifylline, somatostatin analogs, anabolic steroids and androgens, cyclophosphamide, phenyramidol, guanethidine, fluconazole, sulfinpyrazone, tetracyclines, clarithromycin, disopyramide, quinolones, and those drugs that are highly protein-bound, such as fluoxetine, nonsteroidal anti-inflammatory drugs, salicylates, sulfonamides, chloramphenicol, coumarins, probenecid and monoamine oxidase inhibitors. When these medications are administered to a patient receiving Glimepiride, monitor the patient closely for hypoglycemia. When these medications are withdrawn from a patient receiving Glimepiride, monitor the patient closely for worsening glycemic control.

The following are examples of medications that may reduce the glucose-lowering effect of sulfonylureas including Glimepiride, leading to worsening glycemic control: danazol, glucagon, somatropin, protease inhibitors, atypical antipsychotic medications (e.g., olanzapine and clozapine), barbiturates, diazoxide, laxatives, rifampin, thiazides and other diuretics, corticosteroids, phenothiazines, thyroid hormones, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics (e.g., epinephrine, albuterol, terbutaline), and isoniazid. When these medications are administered to a patient receiving Glimepiride, monitor the patient closely for worsening glycemic control. When these medications are withdrawn from a patient receiving Glimepiride, monitor the patient closely for hypoglycemia.

Beta-blockers, clonidine, and reserpine may lead to either potentiation or weakening of Glimepiride's glucose-lowering effect.

Both acute and chronic alcohol intake may potentiate or weaken the glucose-lowering action of Glimepiride in an unpredictable fashion.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

Miconazole
A potential interaction between oral miconazole and sulfonylureas leading to severe hypoglycemia has been reported. Whether this interaction also occurs with other dosage forms of miconazole is not known.

Cytochrome P450 2C9 Interactions
There may be an interaction between glimepiride and inhibitors (e.g., fluconazole) and inducers (e.g., rifampin) of cytochrome P450 2C9. Fluconazole may inhibit the metabolism of glimepiride, causing increased plasma concentrations of glimepiride which may lead to hypoglycemia. Rifampin may induce the metabolism of glimepiride, causing decreased plasma concentrations of glimepiride which may lead to worsening glycemic control.

Concomitant Administration of Colesevelam
Colesevelam can reduce the maximum plasma concentration and total exposure of glimepiride when the two are coadministered. However, absorption is not reduced when glimepiride is administered 4 hours prior to colesevelam. Therefore, Glimepiride should be administered at least 4 hours prior to colesevelam.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C
There are no adequate and well-controlled studies of Glimepiride in pregnant women. In animal studies there was no increase in congenital anomalies, but an increase in fetal deaths occurred in rats and rabbits at glimepiride doses 50 times (rats) and 0.1 times (rabbits) the maximum recommended human dose (based on body surface area). This fetotoxicity, observed only at doses inducing maternal hypoglycemia, is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride and has been similarly noted with other sulfonylureas. Glimepiride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because data suggest that abnormal blood glucose during pregnancy is associated with a higher incidence of congenital abnormalities, diabetes treatment during pregnancy should maintain blood glucose as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers receiving a sulfonylurea at the time of delivery.

Nursing Mothers
It is not known whether Glimepiride is excreted in human milk. During pre- and post-natal studies in rats, significant concentrations of glimepiride were present in breast milk and the serum of the pups. Offspring of rats exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride. Based on these animal data and the potential for hypoglycemia in a nursing infant, a decision should be made whether to discontinue nursing or discontinue Glimepiride, taking into account the importance of Glimepiride to the mother.

Pediatric Use
The pharmacokinetics, efficacy and safety of Glimepiride have been evaluated in pediatric patients with type 2 diabetes as described below. Glimepiride is not recommended in pediatric patients because of its adverse effects on body weight and hypoglycemia.

The pharmacokinetics of a 1 mg single dose of Glimepiride was evaluated in 30 patients with type 2 diabetes (male = 7; female = 23) between ages 10 and 17 years. The mean (± SD) AUC(0-last) (339±203 ng•hr/mL), Cmax (102±48 ng/mL) and t1/2 (3.1±1.7 hours) for glimepiride were comparable to historical data from adults (AUC(0-last) 315±96 ng•hr/mL, Cmax 103±34 ng/mL and t1/2 5.3±4.1 hours).

The safety and efficacy of Glimepiride in pediatric patients was evaluated in a single-blind, 24week trial that randomized 272 patients (8-17 years of age) with type 2 diabetes to Glimepiride (n=135) or metformin (n=137). Both treatment-naïve patients (those treated with only diet and exercise for at least 2 weeks prior to randomization) and previously treated patients (those previously treated or currently treated with other oral antidiabetic medications for at least 3 months) were eligible to participate. Patients who were receiving oral antidiabetic agents at the time of study entry discontinued these medications before randomization without a washout period. Glimepiride was initiated at 1 mg, and then titrated up to 2, 4 or 8 mg (mean last dose 4 mg) through Week 12, targeting a self-monitored fasting fingerstick blood glucose < 126 mg/dL. Metformin was initiated at 500 mg twice daily and titrated at Week 12 up to 1000 mg twice daily (mean last dose 1365 mg).

Geriatric Use
In clinical trials of Glimepiride, 1053 of 3491 patients (30%) were >65 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
There were no significant differences in glimepiride pharmacokinetics between patients with type 2 diabetes ≤65 years (n=49) and those >65 years (n=42).

Glimepiride is substantially excreted by the kidney. Elderly patients are more likely to have renal impairment. In addition, hypoglycemia may be difficult to recognize in the

elderly. Use caution when initiating Glimepiride and increasing the dose of Glimepiride in this patient population.

Renal Impairment
To minimize the risk of hypoglycemia, the recommended starting dose of Glimepiride is 1 mg daily for all patients with type 2 diabetes and renal impairment.

A multiple-dose titration study was conducted in 16 patients with type 2 diabetes and renal impairment using doses ranging from 1 mg to 8 mg daily for 3 months. Baseline creatinine clearance ranged from 10-60 mL/min. The pharmacokinetics of Glimepiride were evaluated in the multiple-dose titration study and the results were consistent with those observed in patients enrolled in a single-dose study. In both studies, the relative total clearance of Glimepiride increased when kidney function was impaired. Both studies also demonstrated that the elimination of the two major metabolites was reduced in patients with renal impairment.

ADVERSE EVENTS

- Hypoglycemia
- Hemolytic anemia

Clinical Trials Experience
Approximately 2,800 patients with type 2 diabetes have been treated with Glimepiride in the controlled clinical trials. In these trials, approximately 1,700 patients were treated with Glimepiride for at least 1 year.

Table 1 summarizes adverse events, other than hypoglycemia, that were reported in 11 pooled placebo-controlled trials, whether or not considered to be possibly or probably related to study medication. Treatment duration ranged from 13 weeks to 12 months. Terms that are reported represent those that occurred at an incidence of ≥5% among Glimepiride -treated patients and more commonly than in patients who received placebo.

Table 1. Eleven Pooled Placebo-Controlled Trials ranging from 13 weeks to 12 months: Adverse Events (Excluding Hypoglycemia) Occurring in ≥5% of Glimepiride -treated Patients and at a Greater Incidence than with Placebo*

	Glimepiride N=745 %	Placebo N=294 %
Headache	8.2	7.8
Accidental Injury†	5.8	3.4
Flu Syndrome	5.4	4.4
Nausea	5.0	3.4
Dizziness	5.0	2.4

* Glimepiride doses ranged from 1-16 mg administered daily †Insufficient information to determine whether any of the accidental injury events were associated with hypoglycemia

Hypoglycemia:
In a randomized, double-blind, placebo-controlled monotherapy trial of 14 weeks duration, patients already on sulfonylurea therapy underwent a 3-week washout period then were randomized to Glimepiride 1 mg, 4 mg, 8 mg or placebo. Patients randomized to Glimepiride 4 mg or 8 mg underwent forced-titration from an initial dose of 1 mg to these final doses, as tolerated. The overall incidence of possible hypoglycemia (defined by the presence of at least one symptom that the investigator believed might be related to hypoglycemia; a concurrent glucose measurement was not required) was 4% for Glimepiride 1 mg, 17% for Glimepiride 4 mg, 16% for Glimepiride 8 mg and 0% for placebo. All of these events were self-treated.

In a randomized, double-blind, placebo-controlled monotherapy trial of 22 weeks duration, patients received a starting dose of either 1 mg Glimepiride or placebo daily. The dose of Glimepiride was titrated to a target fasting plasma glucose of 90-150 mg/dL. Final daily doses of Glimepiride were 1, 2, 3, 4, 6 or 8 mg. The overall incidence of possible hypoglycemia (as defined above for the 14-week trial) for Glimepiride vs. placebo was 19.7% vs. 3.2%. All of these events were self-treated.

Weight gain: Glimepiride, like all sulfonylureas, can cause weight gain

Allergic Reactions: In clinical trials, allergic reactions, such as pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occurred in less than 1% of Glimepiride -treated patients. These may resolve despite continued treatment with Glimepiride. There are postmarketing reports of more serious allergic reactions (e.g., dyspnea, hypotension, shock).

Laboratory Tests: Elevated Serum Alanine Aminotransferase (ALT): In 11 pooled placebo-controlled trials of Glimepiride, 1.9% of Glimepiride -treated patients and 0.8% of placebo-treated patients developed serum ALT greater than 2 times the upper limit of the reference range.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of Glimepiride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Serious hypersensitivity reactions, including anaphylaxis, angioedema, and Stevens-Johnson Syndrome
- Hemolytic anemia in patients with and without G6PD deficiency
- Impairment of liver function (e.g. with cholestasis and jaundice), as well as hepatitis, which may progress to liver failure.
- Porphyria cutanea tarda, photosensitivity reactions and allergic vasculitis
- Leukopenia, agranulocytosis, aplastic anemia, and pancytopenia
- Thrombocytopenia (including severe cases with platelet count less than 10,000/μL) and thrombocytopenic purpura

- Hepatic porphyria reactions and disulfiram-like reactions
- Hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH), most often in patients who are on other medications or who have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone

OVERDOSAGE
An overdosage of Glimepiride, as with other sulfonylureas, can produce severe hypoglycemia. Mild episodes of hypoglycemia can be treated with oral glucose. Severe hypoglycemic reactions constitute medical emergencies requiring immediate treatment. Severe hypoglycemia with coma, seizure, or neurological impairment can be treated with glucagon or intravenous glucose. Continued observation and additional carbohydrate intake may be necessary because hypoglycemia may recur after apparent clinical recovery.

EXPIRY DATE
Do not use later than the date of expiry.

STORAGE
Store protected from moisture at a temperature not exceeding 30°C

PRESENTATION
AZULIX-1, AZULIX-2, AZULIX-3, AZULIX-4 are available as blister strip of 10 tablets.

MARKETED BY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