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ORINASE®
(Glimepiride)

اورینیز

COMPOSITION:
Orinase Tablet 1 mg:
Each tablet contains:
Glimepiride USP ..... 1 mg.

Product Specs.: USP

Orinase Tablet 2 mg:
Each tablet contains:
Glimepiride USP ..... 2 mg.

Product Specs.: USP

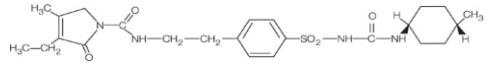
Orinase Tablet 3 mg:
Each tablet contains:
Glimepiride USP ..... 3 mg.

Product Specs.: USP

Orinase Tablet 4 mg:
Each tablet contains:
Glimepiride USP ..... 4 mg.

Product Specs.: USP

DESCRIPTION:
ORINASE is an oral sulfonylurea that contains the active ingredient glimepiride. Chemically, glimepiride is identified as1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea ($C_{24}H_{34}N_4O_5S$) with a molecular weight of 490.62. Glimepiride is a white to yellowish-white, crystalline, odorless to practically odorless powder and is practically insoluble in water.
The structural formula is:



CLINICAL PHARMACOLOGY :
Mechanism of Action: Glimepiride primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Sulfonylureas bind to the sulfonylurea receptor in the pancreatic beta-cell plasma membrane, leading to closure of the ATP-sensitive potassium channel, thereby stimulating the release of insulin.
Pharmacokinetics:
Absorption: With multiple oral doses in patients with type 2 diabetes show peak drug concentrations (C_{max}) 2 to 3 hours post-dose. When glimepiride was given with meals, the mean C_{max} and AUC (area under the curve) may decrease by 8% and 9%, 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 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.
Elimination: When^{14} C-glimepiride was given orally, 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. Approximately 40% of the total radioactivity was recovered in feces. M1 and M2 accounted for about 70% of the radioactivity recovered in feces. No parent drug was recovered from urine or feces.
Pharmacokinetics in Special Populations:
Geriatric Patients: There were no significant differences in glimepiride pharmacokinetics between the younger patients and elderly.
Gender: There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight.
Renal Impairment: Glimepiride serum concentrations decreased with decreasing renal function. The apparent terminal half-life ($t_{1/2}$) 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 decrease.
Hepatic Impairment: Glimepiride has not been adequately evaluated in patients with hepatic impairment.
Obese Patients: The pharmacokinetics of glimepiride and its metabolites like Tmax, clearance, and volume of distribution of glimepiride in the morbidly obese patients are similar to those in the normal weight, the morbidly obese have lower C_{max} and AUC than those of normal body weight.

INDICATIONS AND USAGE:
ORINASE is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Important Limitations of Use: ORINASE should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

DOSAGE and ADMINISTRATION:
ORINASE should be administered with breakfast or the first main meal of the day.
Recommended Dosing: The recommended starting dose of ORINASE 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 ORINASE from longer half-life sulfonylureas (e.g.,chlorpropamide) may have overlapping drug effect for 1-2 weeks and should be appropriately monitored for hypoglycemia.

CONTRAINDICATIONS:
ORINASE 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 ORINASE. Do not use ORINASE in patients who have a history of an allergic reaction to sulfonamide derivatives. 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 ORINASE, can cause severe hypoglycemia. 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 ORINASE 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: Serious reactions such as anaphylaxis, angioedema, and Stevens - Johnson syndrome have been reported with glimepiride. If a hypersensitivity reaction is suspected, promptly discontinue ORINASE, assess for other potential causes for the reaction, and institute alternative treatment for diabetes.
Hemolytic Anemia: Sulfonylureas like Orinase can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (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. Although only one drug in the sulfonylurea class (tolbutamide) was studied for cardiovascular mortality with Sulfonylureas, 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 conclusive evidence of macrovascular risk reduction with glimepiride or any other anti-diabetic drug.

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DRUG INTERACTIONS:
Drugs Affecting Glucose Metabolism:
- ***The following medications may increase the glucose-lowering effect of sulfonylureas including ORINASE, 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 ORINASE, monitor the patient closely for hypoglycemia. When these medications are withdrawn from a patient receiving ORINASE, monitor the patient closely for worsening glycemic control.
- ***The following medications may reduce the glucose-lowering effect of sulfonylureas including ORINASE, 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 ORINASE, monitor the patient closely for worsening glycemic control. When these medications are withdrawn from a patient receiving ORINASE, monitor the patient closely for hypoglycemia.
- Beta-blockers, clonidine, and reserpine may lead to either potentiation or weakening of ORINASE's glucose-lowering effect.
- Both acute and chronic alcohol intake may potentiate or weaken the glucose-lowering action of ORINASE 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.
- 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, ORINASE should be administered at least 4 hours prior to colesevelam.

USE IN SPECIFIC POPULATIONS:
Pregnancy:
Pregnancy Category C:
ORINASE 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.
Nursing Mothers: It is not known whether ORINASE is excreted in human milk. Based on the potential for hypoglycemia in a nursing infant, a decision should be made whether to discontinue nursing or discontinue ORINASE, taking into account the importance of ORINASE to the mother.
Pediatric Use: Not recommended because of adverse effects on body weight and hypoglycemia.
Geriatric Use: Elderly patients are more likely to have renal impairment. In addition, hypoglycemia may be difficult to recognize in the elderly therefore use caution when initiating ORINASE and increasing the dose of ORINASE in this patient population.
Patients with Renal Impairment: To minimize the risk of hypoglycemia, the recommended starting dose of ORINASE is 1 mg daily for all patients with type 2 diabetes and renal impairment. Elimination pharmacokinetics of the two major metabolites was reduced in patients with renal impairment.

ADVERSE REACTIONS:
Most common adverse reactions with ORINASE were hypoglycemia, dizziness, asthenia, headache, and nausea.
Specific:
The following serious adverse reactions are discussed in more detail below and elsewhere in the labeling:
- Hypoglycemia
- Hemolytic anemia

Postmarketing Experience:
The following adverse reactions have been identified during post-approval use of glemipride:
- 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 ORINASE, 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.

INSTRUCTIONS:
- Store below 30ºC.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only

PRESENTATION:

Orinase Tablet 1 mg	:	Pack of 2 x 10 tablets.
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ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

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