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Orinase-Met®

(Glimepiride + Metformin HCl)

اورینیز-میٹ

COMPOSITION:
Orinase-Met 1.0 Tablet:
Each film coated tablet contains:
Glimepiride USP ..... 1 mg.
Metformin HCl BP ..... 500 mg.

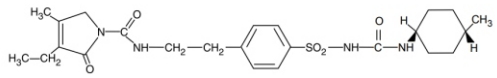
Product Specs.: CCL Pharmaceuticals

Orinase-Met 2.0 Tablet:
Each film coated tablet contains:
Glimepiride USP ..... 2 mg.
Metformin HCl BP ..... 500 mg.

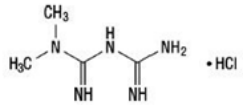
Product Specs.: CCL Pharmaceuticals

DESCRIPTION:
Orinase-Met is a combination or two oral anti-diabetic agents; glimepiride, which is third generation sulfonylurea and metformin hydrochloride which is a biguanide.
Glemipride: The chemical classification of glimepiride is Sulfonylurea as 4-ethyl-3-methyl-N-[2-[4-[(4-methylcyclohexyl)carbamoylsulfamoyl]phenyl]ethyl]-5-oxo-2H-pyrrole-1-carboxamide with a molecular formula $C_{24}H_{34}N_4O_5S$ And molecular weight 490.619 and structural formula:

The structural formula is:



Metformin hydrochloride: Chemically Metformin hydrochloride is Imidodicarbinimidic, N, N-dimethyl-, monohydrochloride, a compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. The structural formula is:



CLINICAL PHARMACOLOGY:
Mechanism of Action:
Sulfonylureas and biguanides act complementary to each other. Both compounds have an additive antihyperglycaemic effect without increasing the adverse effects of either pharmacological class.
Glimepiride is a third generation sulphonylurea. It reduces blood glucose levels by stimulating insulin secretions from the beta cells of pancreas and also known to increase peripheral insulin sensitivity thereby decreasing insulin resistance. There is closing of K+ channels and simultaneously opening of calcium channels giving rise to calcium influx which ultimately results in insulin release from the beta cells of pancreas. Glimepiride also enhances, the glucose sensitivity of the beta cells. Glimepiride improves peripheral insulin sensitivity which increases the glucose clearance and also decreases hepatic glucose production.
Metformin acts by improving hepatic and peripheral tissue sensitivity of insulin and thus it act as an antihyperglycaemic agent. It also has a beneficial effect on the serum lipid profile and has even demonstrated to improve fibrinolytic activity. Metformin therapy does not induce weight gain.
Pharmacokinetics:
Absorption:
Glimepiride is rapidly and completely absorbed after oral administration. The oral bioavailability is approximately 100%.
Metformin has absolute oral bioavailability of 50-60%. GIT absorption is complete within 6 hours of ingestion.
Distribution:
Glimepiride: More than 99% of the drug is bound to plasma proteins.
Metformin: is rapidly distributed in body after absorption.
Metabolism: Glimepiride is completely biotransformed by hepatic oxidative metabolism into cyclohexylhydroxymethyl derivative (M1) which is further metabolized to form a carboxyl derivative (M2) by cytosolic enzymes.
Elimination:
Glimepiride: After a single dose, the elimination half-life ($t_{1/2}$) of Glimepiride is 5 hours. The urinary excretion of metabolites accounts for 60% of dose, the remainder is found as metabolites in faeces.
Metformin: The renal elimination of Metformin is biphasic. 95% of the absorbed Metformin is eliminated during primary elimination phase having half-life of 6 hours. Rest of the 5% is eliminated during slow terminal elimination phase with mean half-life of 20 hours. Metformin is not bound to plasma proteins, 40-60% of the dose is recovered as unchanged drug in urine with a further 30% recovered as unchanged drug in faeces.
Pharmacokinetics in special population:
Geriatric: There were no significant differences in glimepiride pharmacokinetics from the younger age groups. The mean AUC at steady state for the older patients was about 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was about 11% higher than that for the younger patients.
Pediatric: The pharmacokinetics of glimepiride (1 mg) evaluated in a study conducted in Type 2 diabetic patients between ages 10 and 17 years. The mean AUC(0-last), C_{max}, and $t_{1/2}$ were comparable to those previously reported in adults
Gender: There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight.
Renal Insufficiency: Glimepiride serum levels decreased as renal function decreased. The apparent terminal half-life ($t_{1/2}$) for glimepiride did not change, while the half-lives for metabolites increased as renal function decreased. A starting dose of 1 mg glimepiride may be given to Type 2 diabetic patients with kidney disease, and the dose may be titrated based on fasting blood glucose levels.
Hepatic Insufficiency. No studies were performed in patients with hepatic insufficiency.

INDICATIONS AND USAGE:
Glimepiride is used concomitantly with Metformin and is indicated for Type II Diabetes Mellitus (NIDDM) in adults, with or without obesity when diet, exercise, and Glimepiride or Metformin alone does not result in adequate glycemic control.

DOSAGE AND ADMINISTRATION:
The tablet is taken as once daily with meals to a maximum of 4 tablets/day or as directed by the physician.
- Tablets should be swallowed whole and not crushed or chewed.
- Dosage must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended dose.
- The maximum daily dose of Metformin is 2000 mg and of Glimepiride is 8 mg.

CONTRAINDICATIONS:
Insulin-dependent diabetes mellitus, renal or hepatic failure, alcoholism, NIDDM complicated by severe ketosis and acidosis, diabetic pre-coma and coma, patients undergoing surgery, after severe trauma or during infections, chronic obstructive pulmonary disease, coronary heart disease, cardiac failure, peripheral vascular disease, pregnancy, known hypersensitivity to any of the ingredients.

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WARNINGS AND PRECAUTIONS:
Hypoglycaemia may occur if the patient's dietary intake is reduced or after accidental or deliberate overdose or after severe exercise, trauma and stress. Hypoglycaemic symptoms can be reduced by prescribing a diabetic meal plan. Immediate intervention should be done if signs and symptoms of hypoglycaemia occur. Adjust dose of drug according to blood and urinary glucose levels during the first few months. However, there have been few reports of lactic acidosis with Metformin in patients of renal or liver disease.

DRUG INTERACTIONS:
Glimepiride: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as salicylates, sulfonamides, monoamine oxidase inhibitors, and beta adrenergic blocking agents. Co-administration of aspirin and Glimepiride led to a 34% decrease in the mean Glimepiride AUC and, therefore, a 34% increase in the mean CL/f. The mean C_{max} had a decrease of 4%. Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported. Co-administration of either cimetidine (800 mg once daily) or ranitidine (150 mg bid) with a single 4 mg oral dose of Glimepiride did not significantly alter the absorption and disposition of Glimepiride. Concomitant administration of propanolol (40 mg tid) and Glimepiride significantly increased C_{max}, AUC, and t1/2 of Glimepiride by 23%, 22% and 15% respectively, and it decreased CL/f by 18%. Concomitant administration of Glimepiride (4 mg once daily) did not alter the pharmacokinetic characteristics of R - and Swarfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin. The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2 mg Glimepiride were unaffected by co-administration of ramipril (an ACE inhibitor) 5 mg once daily.

DRUG INTERACTIONS:
Metformin: Metformin is seen with phenprocoumon, hyperglycemic agent (e.g.-thiazides, corticosteroids and others), alcohol, furosemide, nifedipine and cationic drugs (amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, cimetidine and vancomycin). The absorption of Metformin may be reduced by acarbose and guar gum.

USE IN SPECIFIC POPULATIONS:
Pregnancy and lactation: The drug should not be used in pregnant women and lactating mothers. They should only be used if potential benefit outweigh the risk involved.
Pediatric use: Safety and effectiveness of the drug in children have not been established.

ADVERSE REACTIONS:
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. Change in accommodation and / or blurred vision may occur. Common adverse reactions in clinical trials (≥ 5% and more common than with placebo) include hypoglycemia, headache, nausea, and dizziness Nausea, diarrhoea, gastric pain, constipation, vomiting metallic taste in mouth Rash, pruritus, urticaria, erythema and flushing. Headache and dizziness impaired gastrointestinal absorption of vitamin B_{12} and folic acid has been associated with long term Metformin therapy. Measurement of serum vitamin B_{12} level is advised on an annual basis as Metformin interfere with B_{12} absorption from intrinsic factor complex.

OVERDOSAGE:
Hypoglycaemia may occur in case of an overdosage. In the event of an overdosage, gastric lavage should be performed and correction of hypoglycaemia should be attempted by intravenous administration of hypertonic glucose (10 or 30%) with continued monitoring of the patient's blood glucose levels. Usual supportive measure should be opted in case of Orinase-Met over dosage.

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

PRESENTATION:

Orinase-Met 1.0 Tablet	:	Pack of 3 x 10 tablets.
Orinase-Met 2.0 Tablet	:	Pack of 3 x 10 tablets.

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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