120mm

181mm

Sitamin Tablet

(Sitagliptin + Metformin HCl)

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. If acidosis is suspected discontinue Sitamin and hospitalize the patient immediately.

سیٹامن ٹیبلیٹ

(سیٹاگلپٹین + میٹفورمین ایچ سی ایل)

COMPOSITION:

Sitamin Tablet 50mg / 500mg

Each film coated tablet contains:

Sitagliptin (as phosphate monohydrate) 50mg

Metformin hydrochloride 500mg

(BP Specification)

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Sitagliptin (as phosphate monohydrate) 50mg

Metformin hydrochloride 1000mg

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DESCRIPTION:

Sitamin is a combination of two oral anti-hyperglycemic agents i.e. sitagliptin and metformin hydrochloride. Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. Metformin is a biguanide anti-hyperglycemic agent used for treating non-insulin-dependent diabetes mellitus (type- 2 diabetes).

MECHANISM OF ACTION:

• ***Sitagliptin***

It is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, Sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner.

• ***Metformin HCl***

It is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia. Metformin HCl may active via three mechanisms;

- By reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- In muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
  By delaying intestinal glucose absorption.

THERAPEUTIC INDICATIONS:

Sitamin (Sitagliptin+ Metformin HCl) is indicated as:

- Initial therapy in patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise do not provide adequate glycemic control.
- As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus inadequately controlled on Metformin HCl or Sitagliptin alone or in patients already being treated with the combination of Sitagliptin and Metformin HCl.
- In triple combination with a sulphonylureas as an adjunct to diet and exercise in patients with type 2 diabetes mellitus inadequately controlled on their maximal tolerated dose of Metformin HCl and a sulphonylureas.
- In triple combination with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of Metformin HCl and a PPARγ agonist.

In patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control in combination with insulin.

DOSAGE AND ADMINISTRATION:

The dosage of Sitamin (Sitagliptin + Metformin HCl) should be individualized on the basis of patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100mg Sitagliptin and 200mg metformin. It should be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects associated with Metformin HCl.

As initial therapy

For patients with type 2 diabetes mellitus, in which hyperglycemia is inadequately controlled with diet and exercise alone.

The recommended starting dose of SITAMIN (Sitagliptin + Metformin HCl) is 50mg of Sitagliptin + 500mg of Metformin HCl twice daily. Patients may be treated upto 50mg Sitagliptin +1000mg of Metformin HCl twice daily.

For patients inadequately controlled on metformin monotherapy

The usual starting dose of SITAMIN (Sitagliptin + Metformin HCl) should provide Sitagliptin dosed as 50mg twice daily (100mg total daily dose), plus Metformin HCl dose already being taken.

For patients inadequately controlled on Sitagliptin monotherapy

The usual starting dose of SITAMIN (Sitagliptin + Metformin HCl) is 50mg Sitagliptin+500mg Metformin HCl twice daily. Patients may be titrated upto 50mg Sitagliptin+1000mg Metformin HCl twice daily.

For patient switching from Sitagliptin co-administered with Metformin HCl

For patients switching from co-administration of Sitagliptin and Metformin HCl, SITAMIN (Sitagliptin+Metformin HCl) may be initiated at the dose of Sitagliptin and Metformin HCl already being taken.

For patients inadequately controlled on dual combination therapy with any two of following three antihyperglycemic agents: sitagliptin, metformin HCl or sulphonylureas.

The usual starting dose of SITAMIN (Sitagliptin + Metformin HCl) should provide Sitagliptin dosed as 50mg twice daily (100mg total daily dose). In determining the starting dose of Metformin HCl component, the patients level of glycemic control and current dose (if any) of Metformin HCl should be considered.

For patients inadequately controlled on dual combination therapy with any two of following three antihyperglycemic agents: Sitagliptin, Metformin HCl or insulin.

The usual starting dose of SITAMIN (Sitagliptin + Metformin HCl) should provide Sitagliptin dosed as 50mg twice daily (100mg total daily dose). 1n determining the starting dose of Metformin HCl component, the patients level of glycemic control and current dose (if any) of Metformin HCl should be considered.

PHARMACOKINETICS:

• **Sitagliptin**

Absorption

Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 μMhr, Cmax was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

Distribution

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38 %).

Biotransformation

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79 % of sitagliptin is excreted unchanged in the urine.

Elimination

Following administration of an oral sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces (13 %) or urine (87 %) within one week of dosing. The apparent terminal t½ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses.

• **Metformin**

Absorption

After an oral dose of metformin, Tmax is reached in 2.5h. Absolute bioavailability of a 500mg metformin tablet given under fasting conditions is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30 %. After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63 – 276 L.

Biotransformation

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

•***Elimination***

Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

PRECAUTIONS:

• ***Monitoring of renal function***

Sitagliptin+Metformin HCl are known to be substantially, excreted by the kidney. Metformin HCl related lactic acidosis increases with the degree of insufficiency of renal function, therefore, serum creatinine concentrations should be determined regularly.

• ***Impaired hepatic function***

Since impaired hepatic function has been associated with some cases of lactic acidosis, Sitagliptin+Metformin HCl should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

• ***Hypoglycemia***

Patient receiving Sitagliptin+Metformin HCl in combination with a Sulphonylurea or with insulin may be at risk for hypoglycemia. Therefore, a reduction in the dose of the sulphonylurea or insulin may be necessary.

• **Sitagliptin**

Pancreatitis

After initiation of Sitagliptin, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, Sitagliptin should promptly be discontinued and appropriate management should be initiated.

• **Metformin HCl**

Lactic acidosis

It is a very rare, but serious, metabolic complication can occur due to Metformin HCl accumulation. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes. Ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalized immediately.

Administration of iodinated contrast agent

The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure which has been associated with lactic acidosis in patients receiving Metformin HCl. Therefore, Sitagliptin+ Metformin HCl should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Pregnancy

The safety of Sitagliptin+Metformin HCl in pregnant women is not known. So like other antihyperglycemic agents, it is not recommended for use in pregnancy.

Nursing Mother

It is not known whether Sitagliptin is excreted in human milk because many drugs are excreted in human milk, Sitagliptin + Metformin HCl should not be administered during nursing.

SIDE EFFECTS:

• ***Sitagliptin with Metformin HCl***

Common: nausea.

Uncommon: somnolence, diarrhea, upper abdominal pain and blood glucose

•***Sitagliptin with Metformin HCl and a PPARγ agonist***

Common: hypoglycemia, headache, diarrhea, vomiting and peripheral edema.

•***Sitagliptin with Metformin HCl and insulin***

Very common: hypoglycemia.

Uncommon: headache and dry mouth.

DRUG INTERACTIONS:

• ***Sitagliptin***

Digoxin

Sitagliptin has a small effect on plasma digoxin concentrations. No dosage adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when Sitagliptin and digoxin are administered concomitantly.

• **Metformin HCl**

Furosemide

Furosemide increased the Metformin HCl plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in Metformin HCl renal clearance.

• ***Nifedipine***

Co-administration of nifedipine increased plasma Metformin HCl Cmax and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. Tmax and half-life were unaffected. Nifedipine appears to enhance the absorption of Metformin HCl. Metformin HCl had minimal effects on nifedipine.

• ***Cationic drugs***

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with Metformin HCl by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of Sitagliptin+Metformin HCl and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

CONTRAINDICATIONS:

The combination of Sitagliptin and Metformin HCl is contraindicated in:

- Patients with type 1 diabetes.
- Renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels ≥1.5mg/dL (males) ≥1.4mg/dL (females), or abnormal creatinine clearance, which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
- Patients with known hypersensitivity to Sitagliptin, Metformin HCl or any other component of the product.
- Acute or chronic metabolic acidosis, including ketoacidosis, with or without coma.
- Children below 18 years of age.

OVERDOSAGE:

• ***Sitagliptin***

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtain an electrocardiogram) and institute supportive therapy as dictated by the patient's clinical status. Sitagliptin is modestly dialyzable. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if Sitagliptin is dialyzable by peritoneal dialysis.

Metformin HCl

In case of Metformin HCl overdose (greater than 50g), hypoglycemia was reported in approximately 10% of cases but no causal association with Metformin HCl has been established. Metformin HCl is dialyzable with a clearance of up to 170mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom Metformin HCl over dosage is suspected.

STORAGE & INSTRUCTIONS:

Store between 15-25°C.

Protect from heat, sunlight & moisture.

Keep away from the reach of children.

To be sold on the prescription of a registered medical practitioner only.

HOW SUPPLIED:

Sitamin Tablet 50mg/500mg

10's ,14's, 30's Tablets.

Sitamin Tablet 50mg/1000mg

10's, 14's Tablets.

خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Manufactured by:

PHARMASOL PRIVATE LIMITED

Plot # 549, Sundar Industrial Estate, Lahore, Pakistan.