SITA-Met®

(Sitagliptin + Metformin HCl)

Tablet

سیٹا-میٹ

COMPOSITION:

SITA-Met 50/500 Tablet:
Each film coated tablet contains:
Sitagliptin phosphate monohydrate equivalent to
Sitagliptin USP ..... 50 mg.
Metformin HCl BP ..... 500 mg.

Product Specs.: BP

SITA-Met 50/850 Tablet:
Each film coated tablet contains:
Sitagliptin phosphate monohydrate equivalent to
Sitagliptin USP ..... 50 mg.
Metformin HCl BP ..... 850 mg.

Product Specs.: BP

SITA-Met 50/1000 Tablet:
Each film coated tablet contains:
Sitagliptin phosphate monohydrate equivalent to
Sitagliptin USP ..... 50 mg.
Metformin HCl BP ..... 1000 mg.

Product Specs.: BP

DESCRIPTION:

SITA-MET (sitagliptin and metformin HCl) tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: Sitagliptin and metformin hydrochloride.
Sitagliptin: Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. Sitagliptin is present in SITA-Met tablets in the form of sitagliptin phosphate monohydrate. Sitagliptin phosphate monohydrate is described chemically as 7-[(3R)- 3-amino-1-oxo-4-(2,4,5-trifluorophenyl) butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate with an empirical formula of $C_{16}H_{15}F_6N_5O{\cdot}H_3PO_4{\cdot}H_2O$ and a molecular weight of 523.32.
Metformin hydrochloride: Metformin hydrochloride is a compound with a molecular formula of $C_4H_{11}N_5{\cdot}HCl$ and a molecular weight of 165.63.

CLINICAL PHARMACOLOGY:

Mechanism of action: SITA-Met tablets combine two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in adults with type 2 diabetes mellitus: sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.
Sitagliptin: Sitagliptin is a DPP-4 inhibitor, which exerts its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones.
Metformin hydrochloride: Metformin is a biguanide that improves glycemic control in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose.
Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.
Pharmacokinetics:
Absorption:
Sitagliptin: After oral administration of a 100 mg dose to healthy subjects, sitagliptin is rapidly absorbed with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post dose.
The absolute bioavailability of sitagliptin is approximately 87%.
Metformin hydrochloride: The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50-60%.
Food decreases the extent of and slightly delays the absorption of metformin.
Distribution:
Sitagliptin: The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters.
Metformin hydrochloride: Distribution volume of immediate-release metformin hydrochloride tablets 850 mg averaged 654 ± 358 L.
Elimination:
Sitagliptin: Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination.
The apparent terminal t½ following a 100 mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.
Metformin hydrochloride: Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours.
Metabolism:
Sitagliptin: Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin.
In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.
Metformin hydrochloride: Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion.
Excretion:
Sitagliptin: Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion.
Metformin hydrochloride: Elimination of metformin occurs primarily via renal excretion.
Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination.
Specific Populations:
Patients with renal impairment:
Sitagliptin: An approximately 2-fold increase in the plasma AUC of sitagliptin observed in patients with moderate renal impairment with eGFR of 30 to less than 45 mL/min/1.73 m^2, and an approximately 4-fold increase observed in patients with severe renal impairment including patients with end-stage renal disease (ESRD) on hemodialysis, as compared to normal healthy control subjects.
Metformin hydrochloride: In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased.
Patients with hepatic impairment:
Sitagliptin: In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100-mg dose of sitagliptin.
Metformin hydrochloride: No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

INDICATIONS AND USAGE: SITA-Met is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate.
Important limitations of use: SITA-Met should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using

DOSAGE AND ADMINISTRATION:
Give twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal effects due to metformin. Individualize the starting dose of based on the patient's current regimen. Adjust the dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin. Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR).

DOSE MODIFICATION RECOMMENDATIONS:
Use in renal impairment: Assess renal function prior to initiation of SITA-Met and periodically thereafter. SITA-Met is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2.
SITA-Met is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m^2.
Discontinuation for iodinated contrast imaging procedures: Discontinue SITA-Met at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Reevaluate eGFR 48 hours after the imaging procedure; restart SITA-Met if renal function is stable.

CONTRAINDICATIONS:
SITA-Met (sitagliptin and metformin HCl) is contraindicated in patients with: Severe 2 renal impairment (eGFR below 30 mL/min/1.73 m^2). Hypersensitivity to metformin hydrochloride. Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin. History of a serious hypersensitivity reaction to SITA-Met or sitagliptin (one of the components of SITA-Met), such as anaphylaxis or angioedema.

WARNINGS AND PRECAUTIONS:
Lactic acidosis: Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. If lactic acidosis is suspected, discontinue SITA-Met and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue SITA-Met. Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms Before initiating SITA-Met and at least annually thereafter, assess renal function.
Vitamin B_{12} deficiency: Metformin may lower Vitamin B_{12} levels. Measure hematologic parameters annually. When used with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia. In case of serious allergic and hypersensitivity reactions in patients treated with promptly stop SITA-Met, assess for other potential causes, and institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue SITA-Met.

DRUG INTERACTIONS: Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. Drugs that reduce metformin clearance.
Alcohol: can potentiate the effect of metformin on lactate metabolism.
Insulin Secretagogues or Insulin: Co-administration of SITA-Met with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Use of metformin with other drugs: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control.

USE IN SPECIFIC POPULATIONS:
Pregnancy: The limited available data with Sitagliptin/ Metformin Hydrochloride preparation use in pregnant women.
Lactation: There is no information regarding the presence of SITA-Met in human milk, the effects on the breastfed infant.
Pediatric use: Safety and effectiveness of SITA-Metin pediatric patients under 18 years have not been established.
Geriatric use: Assess renal function more frequently.
Patients with renal impairment: SITA-Met: The dose of the sitagliptin component should be limited to 50 mg once daily if eGFR falls below 45 mL/min/1.73 m^2.
SITA-Met is contraindicated in severe renal impairment, patients with an eGFR below 30 mL/min/1.73 m^2.
Patients with hepatic impairment: SITA-Met is not recommended in patients with hepatic impairment.

ADVERSE REACTIONS:
The most common adverse reactions reported in ≥5% of patients simultaneously started on sitagliptin and metformin were diarrhea,upper respiratory tract infection, and headache. Adverse reactions reported in ≥ 5% of patients treated with sitagliptin in combination with sulfonylurea and metformin were hypoglycemia and headache. Hypoglycemia was the only adverse reaction reported in ≥5% of patients treated with sitagliptin in combination with insulin.
Post marketing experience: Additional adverse reactions have been identified during post marketing use of combination, sitagliptin, or metformin. Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome, upper respiratory tract. infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis, worsening renal function, including acute renal failure (sometimes requiring dialysis), severe and disabling arthralgia, bullous pemphigoid, constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus; mouth ulceration; stomatitis; cholestatic, hepatocellular, and mixed hepatocellular liver injury.

OVERDOSAGE:
Sitagliptin: In the event of an overdose, it is reasonable to employ the usual supportive measures It is not known if sitagliptin is dialyzable by peritoneal dialysis.
Metformin hydrochloride: Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

INSTRUCTIONS:
– Store below 30°C.
– 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:

SITA-Met 50/500 Tablet	:	Pack of 2 x 7 tablets.
SITA-Met 50/850 Tablet	:	Pack of 2 x 7 tablets.
SITA-Met 50/1000 Tablet	:	Pack of 2 x 7 tablets.

Manufactured by:
CCL Pharmaceuticals (Pvt.) Ltd.
Plot No. 710, Sundar Industrial Estate, Raiwind Road Lahore, Pakistan.

FOR FURTHER INFORMATION PLEASE CONTACT:

CCL
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گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

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