Front

SITA-Met XR®

(Sitagliptin + Metformin HCl Extended Release)

سیٹا-میٹ ایکس آر

COMPOSITION:

SITA-Met XR 50/500 Tablet:
Each film coated tablet contains:
Sitagliptin phosphate monohydrate equivalent to
Sitagliptin ..... 50 mg.
Metformin HCl BP (extended release) ..... 500 mg.

Product Specs.: Innovator

SITA-Met XR 50/1000 Tablet:
Each film coated tablet contains:
Sitagliptin phosphate monohydrate equivalent to
Sitagliptin ..... 50 mg.
Metformin HCl BP (extended release) ..... 1000 mg.

Product Specs.: Innovator

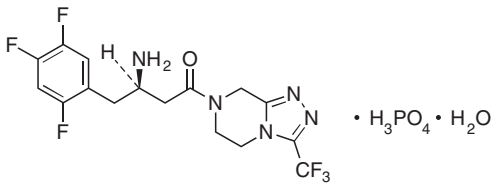
SITA-Met XR 100/1000 Tablet:
Each film coated tablet contains:
Sitagliptin phosphate monohydrate equivalent to
Sitagliptin ..... 100 mg.
Metformin HCl BP (extended release) ..... 1000 mg.

Product Specs.: Innovator

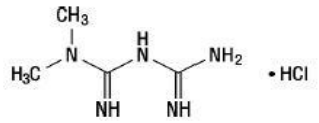
DESCRIPTION:

SITA-Met XR tablets contain two oral antidiabetic medications used in the management of type 2 diabetes:
sitagliptin and metformin hydrochloride extended-release. SITA-Met XR consists of an extended-release metformin core tablet coated with an immediate-release layer of sitagliptin.

Sitagliptin: Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. 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-α] 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. The structural formula is:



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. The structural formula is as shown:



CLINICAL PHARMACOLOGY:

Mechanism of Action:
SITA-Met XR 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 extended-release, 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. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP-4. 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. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.

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. Metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or healthy subjects except in certain circumstances and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacokinetics:
After administration of two SITA-Met XR 50 mg/1000 mg tablets once daily with the evening meal for 7 days in healthy adult subjects, steady-state for sitagliptin and metformin is reached by Day 4 and 5.

Absorption: After administration of SITA-Met XR tablets, the median Tmax value for sitagliptin and metformin at steady state is approximately 3 and 8 hours postdose, respectively. The median T_{max} value for sitagliptin and metformin after administration of a single tablet of SITA-Met XR is 3 and 3.5 hours postdose, respectively.

Effect of Food: After administration of SITA-Met XR tablets with a high-fat breakfast, the AUC for sitagliptin is not altered.
The mean Cmax decrease by 17%, although the median Tmax is unchange relative to the fasted state. After administration of SITA-Met XR with a high-fat breakfast, the AUC for metformin increase 62%, the C_{max} for metformin decreased by 9%, and the median T_{max} for metformin occurrs 2 hours later relative to the fasted state.

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 postdose. The absolute bioavailability of sitagliptin is approximately 87%.

Effect of Food: Co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin.

Metformin hydrochloride: The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%.

Effect of Food: Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850-mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

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. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Metformin hydrochloride: Distribution volume of immediate-release metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Steady-state plasma concentrations of metformin are reached within 24-48 hours and are generally < 1 mcg/mL.

Elimination:

Sitagliptin: Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. The apparent terminal $t_{1/2}$ 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. In blood, the elimination half -life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Metabolism:

Sitagliptin: Following a [14C] sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of 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 (no metabolites have been identified in humans) or biliary excretion. Metabolism studies with extended-release metformin tablets have not been conducted.

Excretion:

Sitagliptin: Following administration of an oral [14C] sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. 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. These differences are not considered to be clinically meaningful. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score >9)

Metformin hydrochloride: No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Effects of Age, Body Mass Index (BMI), Gender, and Race:

Sitagliptin: Based on a population pharmacokinetic analysis of BMI, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of sitagliptin.

Metformin hydrochloride: Pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects.

Pediatric Patients:

Sitagliptin: Studies characterizing the pharmacokinetics of sitagliptin in pediatric patients have not been performed.

INDICATIONS AND USAGE:
SITA-Met XR 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 extended-release is appropriate.

Important Limitations of Use:

- SITA-Met XR should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- SITA-Met XR has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using SITA-Met XR.

DOSAGE AND ADMINISTRATION:

Recommended Dosing:

- The dose of SITA-Met XR should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin.
- In patients not currently treated with metformin, the recommended total daily starting dose of SITA-Met XR is 100 mg sitagliptin and 1000 mg metformin hydrochloride (HCl) extended-release. Patients with inadequate glycemic control on this dose of metformin can be titrated gradually, to reduce gastrointestinal side effects associated with metformin, up to the maximum recommended daily dose.
- In patients already treated with metformin, the recommended total daily starting dose of SITA-Met XR is 100 mg sitagliptin and the previously prescribed dose of metformin.
- For patients taking metformin immediate-release 850 mg twice daily or 1000 mg twice daily, the recommended starting dose of SITA-Met XR is two 50 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablets taken together once daily.
- SITA-Met XR should be administered with food to reduce the gastrointestinal side effects associated with the metformin component.
- SITA-Met XR should be given once daily with a meal preferably in the evening.
- SITA-Met XR should be swallowed whole. The tablets must not be split, crushed, or chewed before swallowing.

Administration:

- SITA-Met XR 100 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablet should be taken as a single tablet once daily.
- SITA-Met XR tablets 50 mg sitagliptin/500 mg metformin hydrochloride extended-release tablets should take the two tablets together once daily (patients taking 2 tablets daily).
- SITA-Met XR 50 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablets) should take the two tablets together once daily (patients taking 2 tablets daily).

DOSE MODIFICATION RECOMMENDATIONS:

Recommendations for Use in Renal Impairment:
Assess renal function prior to initiation of SITA-Met XR and periodically thereafter. SITA-Met XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2. Discontinue SITA-Met XR if the patient's eGFR later falls below 30 mL/min/1.73 m^2. Initiation of SITA-Met XR in patients with an eGFR between 30 and 45 mL/min/1.73 m^2 is not recommended. In patients taking SITA-Met XR whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit risk of continuing therapy and limit dose of the sitagliptin component to 50 mg once daily.

Discontinuation for Iodinated Contrast Imaging Procedures:
Discontinue SITA-Met XR 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^2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart SITA-Met XR if renal function is stable.

CONTRAINDICATIONS:

SITA-Met XR is contraindicated in patients with:

- Severe 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 XR or sitagliptin, such as anaphylaxis or angioedema.

WARNINGS AND PRECAUTIONS:

- Risk of developing Lactic acidosis
- Risk of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis in patients treated with sitagliptin. If pancreatitis is suspected, promptly discontinue.
- Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of SITA-Met XR in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms.
- Risk of Acute renal failure in patients treated with sitagliptin, sometimes requiring dialysis. Assess renal function Before initiating SITA-Met XR and at least annually thereafter,
- 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 minimize the risk of hypoglycemia.
- Risk of serious allergic and hypersensitivity reactions in patients treated with sitagliptin, such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly stop SITA-Met XR, 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.
- Risk 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 XR.
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with SITA-Met XR.

DRUG INTERACTIONS:

Carbonic Anhydrase Inhibitors: Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use with SITA-Met XR may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.

Drugs that Reduce Metformin Clearance: Concomitant use of drugs that interfere with renal elimination of metformin (e.g., organic cationic transporter -2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis.

Alcohol: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving SITA-Met XR.

Insulin Secretagogues or Insulin: Co-administration of SITA-Met XR 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. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. Patient should be closely observed to maintain adequate glycemic control.

Digoxin: Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or SITA-Met XR is recommended.

USE IN SPECIFIC POPULATIONS:

Pregnancy: The limited available data with Sitagliptin/ Metformin Hydrochloride XR preparation use in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage.

Lactation: There is no information regarding the presence of SITA-Met XR in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breast feeding should be considered along with the mother's clinical need for SITA-Met XR and any potential adverse effects on the breastfed infant from SITA-Met XR or from the underlying maternal condition.

Pediatric Use: Safety and effectiveness of SITA-Met XR in pediatric patients under 18 years have not been established.

Geriatric Use: Assess renal function more frequently

Patients with Renal Impairment:

SITA-Met XR: 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 XR is contraindicated in severe renal impairment, patients with an eGFR below 30 mL/min/1.73 m^2.

Patients with Hepatic Impairment: Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. SITA-Met XR 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 and more commonly than in patients treated with placebo were diarrhea, upper respiratory tract infection, and headache.
- Adverse reactions reported in ≥ 5% of patients treated with sitagliptin in combination with sulfonylurea and metformin and more commonly than in patients treated with placebo 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 and metformin and more commonly than in patients treated with placebo in combination with insulin and metformin.

Postmarketing Experience: Additional adverse reactions have been identified during postapproval use of sitagliptin with metformin, sitagliptin, or metformin including 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, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy as indicated by the patient's clinical status. Prolonged hemodialysis may be considered if clinically appropriate. 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 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:

SITA-Met XR 50/500 Tablet	:	Pack of 2 x 7 tablets.
SITA-Met XR 50/1000 Tablet	:	Pack of 2 x 7 tablets.
SITA-Met XR 100/1000 Tablet	:	Pack of 2 x 7 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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