Treviamet™ XR

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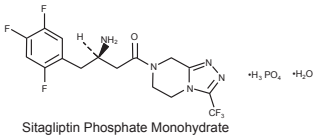
[SITAGLIPTIN+METFORMIN HCl]

Tablets 50mg + 500mg & 50mg + 1000mg

DESCRIPTION

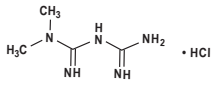
Treviamet XR (Sitagliptin + Metformin HCl) tablets contain two oral antidiabetic medications used in the management of type 2 diabetes; Sitagliptin and Metformin HCl (extended release).

Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzymes. Chemically, it is 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. Its molecular formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the structural formula is:



Sitagliptin Phosphate Monohydrate

Metformin HCl (N,N-dimethylimidodicarbonimidic diamide hydrochloride). Its molecular formula is $C_4H_{11}N_5.HCl$ and the structural formula is:



Metformin HCl

QUALITATIVE & QUANTITATIVE COMPOSITION

Treviamet XR (Sitagliptin + Metformin HCl) is available for oral administration as:

Treviamet XR Tablets 50mg + 500mg
Each tablet contains:
Sitagliptin Phosphate Monohydrate equivalent to Sitagliptin…50mg
Metformin HCl USP...500mg
(as extended release)

Treviamet XR Tablets 50mg + 1000mg
Each tablet contains:
Sitagliptin Phosphate Monohydrate equivalent to Sitagliptin…50mg
Metformin HCl USP...1000mg
(as extended release)

CLINICAL PHARMACOLOGY

Mechanism of Action

Sitagliptin
It is a DPP-4 inhibitor, which exerts 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
Metformin HCl is a biguanide that improves glycemic control in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin HCl decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Pharmacokinetics

Absorption
Sitagliptin
The absolute bioavailability of sitagliptin is approximately 87%. Co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin.

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

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

Metformin HCl
Metformin HCl is negligibly bound to plasma proteins. At usual clinical doses and dosing schedules of metformin HCl, steady-state plasma concentrations of metformin HCl are reached within 24-48 hours and are generally <1mcg/mL.

Metabolism
Sitagliptin
Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination.

Metformin HCl
Intravenous single-dose studies in normal subjects demonstrate that metformin HCl is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion.

Excretion
Sitagliptin
The apparent terminal $t_{1/2}$ following a 100mg oral dose of sitagliptin is approximately 12.4 hours and renal clearance is approximately 350mL/min. Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion.

Metformin HCl
Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin HCl elimination. 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.

Special Population

Elderly Patients
Sitagliptin
Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Metformin HCl
Total plasma clearance of metformin HCl in elderly subjects is decreased, $t_{1/2}$ is prolonged and C_{max} is increased. Treatment should not be initiated in geriatric patients unless measurement of creatinine clearance demonstrates that renal function is normal.

Children under 18 years
Safety and effectiveness of sitagliptin + metformin HCl in children under 18 years have not been established.

THERAPEUTIC INDICATIONS

Treviamet XR (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, when dual sitagliptin and metformin HCl therapy is appropriate (i.e. high initial HbA1c levels and poor prospects of response to monotherapy).
- As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus inadequately controlled on sitagliptin or metformin HCl alone or in patients already being treated with the combination of sitagliptin and metformin HCl.
- In combination with a sulphonylurea as an adjunct to diet and exercise in patients with type 2 diabetes mellitus when combination therapy with metformin HCl and sulphonylurea does not provide adequate glycemic control.
- As an adjunct to diet and exercise to improve glycemic control in combination with insulin in patients with type 2 diabetes mellitus inadequately controlled on insulin and metformin HCl or in patients already being treated with the combination of sitagliptin, metformin HCl and insulin.

DOSAGE AND ADMINISTRATION

General
The dosage of Treviamet XR (Sitagliptin + Metformin HCl) should be individualized on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100mg sitagliptin and 2000mg metformin HCl.
Treviamet XR (Sitagliptin + Metformin HCl) should be given once daily with a meal preferably in the evening. The dose should be escalated gradually to reduce the gastrointestinal (GI) side effects due to metformin HCl.
For patients using 50mg sitagliptin + 500mg metformin HCl extended release tablet or the 50mg sitagliptin + 1000mg metformin HCl extended release tablet, two tablets should be taken together once daily.

As initial therapy
For patients with type 2 diabetes mellitus, whose hyperglycemia is inadequately controlled with diet and exercise alone, when dual therapy is appropriate, the recommended total daily starting dose of Treviamet XR is 100mg sitagliptin and 1000mg metformin HCl.

For patients inadequately controlled on sitagliptin monotherapy
For patients inadequately controlled on sitagliptin alone, the recommended starting dose of Treviamet XR is 100mg sitagliptin and 1000mg metformin HCl daily.

For patients inadequately controlled on metformin HCl monotherapy
For patients not adequately controlled on metformin HCl alone, the usual starting dose of Treviamet XR should provide sitagliptin 100mg total daily dose plus the dose of metformin HCl already being taken.

For patients switching from sitagliptin coadministered with metformin HCl
For patients switching from sitagliptin coadministrated with metformin HCl, Treviamet XR may be initiated at the dose of sitagliptin and metformin HCl already being taken.

For patients inadequately controlled on dual combination therapy with metformin HCl and a sulphonylurea
The usual starting dose of Treviamet XR should provide sitagliptin 100mg total daily dose and the dose of metformin HCl already being taken.

For patients inadequately controlled on dual combination therapy with metformin HCl and insulin
The usual starting dose of Treviamet XR should provide 100mg total daily dose of sitagliptin. In determining the starting dose of the metformin HCl component, the patient's level of glycemic control and current dose of metformin HCl should be considered.

ADVERSE REACTIONS

Sitagliptin with Metformin HCl
Diarrhea, upper respiratory tract infections and headache.

Sitagliptin with Metformin HCl and Sulphonylurea
Hypoglycemia and headache.

Sitagliptin with Metformin HCl and Insulin
Hypoglycemia.

Additional adverse reactions of sitagliptin with or without metformin HCl and/or in combination with other antidiabetic medications include 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, arthralgia, myalgia, pain in extremity, back pain, pruritis, cholestatic, hepatocellular and mixed hepatocellular liver injury.

CONTRAINDICATIONS
Sitagliptin + Metformin HCl is contraindicated in patients with:
- Known hypersensitivity to sitagliptin and metformin HCl or to any of excipient of the product.
- Renal disease or renal dysfunction, e.g. as suggested by serum creatinine levels ≥133 micromol/L [males] or ≥124 micromol/L [females], or abnormal creatinine clearance (<60 mL/min), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction and septicaemia.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosi, with or without coma.

PRECAUTIONS
Lactic acidosis
Metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio and metformin plasma levels generally >5 mcg/mL. If lactic acidosis is suspected, discontinue sitagliptin + metformin HCl and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

Pancreatitis
After initiation of sitagliptin + metformin HCl, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, sitagliptin + metformin HCl should promptly be discontinued and appropriate management should be initiated.

Impaired Hepatic Function
Sitagliptin + metformin HCl should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Heart Failure
An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes. Consider the risks and benefits of sitagliptin + metformin HCl, prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment and observe these patients for signs and symptoms of heart failure during therapy. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of sitagliptin + metformin HCl.

Assessment of Renal Function
Before initiation of therapy with sitagliptin + metformin HCl and at least annually thereafter, renal function should be assessed. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and sitagliptin + metformin HCl discontinued if evidence of renal impairment is present.

Vitamin B_{12} Levels
Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B_{12} measurements at two to three years intervals may be useful.

Alcohol Intake
Alcohol potentiates the effect of metformin HCl on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving sitagliptin + metformin HCl.

Surgical Procedures
Use of sitagliptin + metformin HCl should be temporarily discontinued while patients have restricted food and fluid intake. Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes
If acidosis of either form (ketoacidosis & lactic acidosis) occurs, sitagliptin + metformin HCl must be stopped immediately and other appropriate corrective measures initiated. Evaluation should include serum electrolytes and ketones, blood glucose and if indicated, blood pH, lactate, pyruvate and metformin HCl levels.

Use with Medications Known to Cause Hypoglycemia
A lower dose of insulin or sulphonylurea may be required to reduce the risk of hypoglycemia.

Concomitant Medications Affecting Renal Function or Metformin HCl Disposition
The concomitant use of sitagliptin + metformin HCl with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation. Therefore, consider more frequent monitoring of patients.

Radiologic Studies with Intravascular Iodinated Contrast Materials
Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop sitagliptin + metformin HCl at the time of, or prior to, an iodinated contrast imaging procedure. Re-evaluate eGFR 48 hours after the imaging procedure and restart sitagliptin + metformin HCl if renal function is stable.

Hypoxic States
When cardiovascular collapse, acute myocardial infarction or sepsis occur in patients on sitagliptin + metformin HCl therapy, the drug should be promptly discontinued.

Hypersensitivity Reactions
If a hypersensitivity reaction is suspected, discontinue sitagliptin + metformin HCl, assess for other potential causes for the event and institute alternative treatment for diabetes.

Pregnancy
There are no adequate and well-controlled studies in pregnant women with sitagliptin + metformin HCl. Therefore, sitagliptin + metformin HCl should be used during pregnancy only if clearly needed.

Nursing Mother
It is not known whether sitagliptin + metformin HCl is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when administered to a nursing woman.

DRUG INTERACTIONS
Carbonic Anhydrase Inhibitors
Concomitant use of carbonic anhydrase inhibitors may induce metabolic acidosis. Use these drugs with caution in patients treated with sitagliptin + metformin HCl, as the risk of lactic acidosis may increase and consider more frequent monitoring of these patients.

Drugs that Reduce Metformin Clearance
Concomitant use of drugs that interfere with common renal tubular transport systems involved in the 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. Consider the benefits and risks of concomitant use.

Use of Metformin HCl with other drugs
Certain medicines 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. When such drugs are administered to a patient receiving sitagliptin + metformin HCl, the patient should be closely observed to maintain adequate glycemic control.

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. 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 casual association with metformin HCl has been established. Metfromin 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 overdosage is suspected.

STORAGE
Do not store above 30°C.
Protect from sunlight & moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Treviamet XR (Sitagliptin + Metformin HCl) Tablets 50mg + 500mg are available in pack of 14's.
Treviamet XR (Sitagliptin + Metformin HCl) Tablets 50mg + 1000mg are available in pack of 14's.

Keep out of reach of children.

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

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
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