Treviamet™

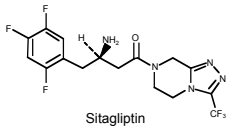
[SITAGLIPTIN + METFORMIN HCl TABLETS]

Tablets 50mg+500mg, 50mg+1000mg

DESCRIPTION

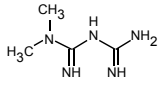
TREVIAMET (Sitagliptin+Metformin HCl) contains two oral antihyperglycemic agents with complementary mechanism of action to improve glycemic control with type 2 diabetes.

Sitagliptin is an orally-active, potent, and highly selective 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

Metformin HCl (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral anti-hyperglycemic agents. It has a molecular formula of $C_4H_{11}N_5$.HCl and the structural formula is:



Metformin HCl

QUALITATIVE & QUANTITATIVE COMPOSITION

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

1. TREVIAMET Tablets 50mg+500mg
   Each film-coated tablet contains:
   Sitagliptin phosphate monohydrate equivalent to
   Sitagliptin … 50mg
   Metformin HCl USP...500mg

2. TREVIAMET Tablets 50mg+1000mg
   Each film-coated tablet contains:
   Sitagliptin phosphate monohydrate equivalent to
   Sitagliptin …50mg
   Metformin HCl USP...1000mg

CLINICAL PHARMACOLOGY

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.

Pharmacokinetics

Absorption

Sitagliptin

Following oral administration of a 100mg dose, Sitagliptin absorbs rapidly with peak plasma concentration (median T_{max}) occurring 1 to 4 hours post-dose, mean plasma AUC of Sitagliptin is 8.52 µM•hr, with C_{max} 950nM. The absolute bioavailability of Sitagliptin is approximately 87%. Plasma AUC of Sitagliptin increased in a dose-proportional manner.

Metformin HCl

After an oral dose of Metformin HCl, T_{max} is reached in 2.5hrs. The absolute bioavailability of a single dose 500mg dose is reported to be about 50% to 60% given under fasting condition. Single oral doses of Metformin hydrochloride tablets 500mg to 1500mg, that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent 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). The pharmacokinetics of Metformin HCl absorption is non-linear.

Distribution

Sitagliptin

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

Metformin HCl

Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of Metformin hydrochloride tablets, steady-state plasma concentrations of Metformin are reached within 24-48 hours and are generally < 1 mcg/mL. Maximum Metformin HCl plasma levels do not exceed 5mcg/mL, even at maximum doses.

Metabolism & Excretion

Sitagliptin

Sitagliptin is primarily eliminated unchanged in urine (approximately 79%), and metabolism is a minor pathway. Following administration of an oral [^{14}C] Sitagliptin dose, approximately 100% of the administered radioactivity eliminate in feces (13%) or urine (87%) within one week of dosing. 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.

Metformin HCl

Metformin HCl is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. 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 24hours, with a plasma elimination half-life of approximately 6.2hours. In blood, the elimination half life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations

Renal Insufficiency

Sitagliptin

Patients with mild renal insufficiency did not have a clinically meaningful increase in the plasma concentration of Sitagliptin. The plasma AUC of Sitagliptin increases approximately 2-fold in patients with moderate renal insufficiency, and an approximately 4-fold in patients with severe renal insufficiency and in patients with ESRD on hemodialysis.

Metformin HCl

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of Metformin HCl is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Insufficiency

Sitagliptin

There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score> 9). However, because Sitagliptin is primarily renally eliminated, severe hepatic insufficiency is not expected to affect the pharmacokinetics of Sitagliptin.

Metformin HCl

No pharmacokinetic studies of Metformin HCl have been conducted in patients with hepatic insufficiency.

Elderly

Sitagliptin

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

Metformin HCl

Incase of elderly patients renal function of Metformin HCl is impaired, resulting in decreased total plasma clearance, prolonged $t_{1/2}$, and increased Cmax. So, it is recommended not to initiate Sitagliptin + Metformin HCl in geriatric patient ≥ 80years without monitoring renal function.

Pediatric

No studies with Sitagliptin + Metformin HCl have been performed in pediatric population.

THERAPEUTIC INDICATIONS

TREVIAMET (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 sulphonylurea 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 sulphonylurea.
- 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 TREVIAMET (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.

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, whose hyperglycemic is inadequately controlled with diet and exercise alone, the recommended starting dose of TREVIAMET (Sitagliptin + Metformin HCl) is 50mg of Sitagliptin + 500mg of Metformin HCl twice daily. Patients may be titrated upto 50mg Sitagliptin + 1000mg of Metformin HCl twice daily.

For patients inadequately controlled on metfomrin monotherapy

The usual starting dose of TREVIAMET (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 TREVIAMET (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, TREVIAMET (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 PPARγ agonist (thiazolidinedione).
The usual starting dose of TREVIAMET (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 sulphonylurea.
The usual starting dose of TREVIAMET (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 TREVIAMET (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.

ADVERSE REACTIONS
Sitagliptin with Metformin HCl
Common: nausea.
Uncommon: somnolence, diarrhea, upper abdominal pain and blood glucose decreased.

Sitagliptin with Metformin HCl and Sulphonylurea
Very common: hypoglycemia
Common: constipation.

Sitagliptin with Metformin HCl and a PPARγ agonist
Common: hypoglycemia, headache, diarrhea, vomiting, peripheral edema.

Sitagliptin with Metformin HCl and insulin
Very common: hypoglycemia.
Uncommon: headache, dry mouth.

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.
- Known hypersensitivity to Sitagliptin, Metformin HCl or any other component of Sitagliptin+Metformin HCl.
- Acute or chronic metabolic acidosis , including ketoacidosis, with or without coma.
- Children below 18 years of age.

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 +metfomrin HCl should not be administered during nursing.

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 hospitalised 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.

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 C_{max} 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.

Other
Certain medicines tend to produce hyperglycaemia and may lead to loss of glycaemic 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 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
Incase 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. 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
Store below 30°C.
Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
TREVIAMET (Sitagliptin + Metformin HCl) Tablets 50mg+500mg are available in blister packs of 14's.

TREVIAMET (Sitagliptin + Metformin HCl) Tablets 50mg+1000mg are available in blister packs 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.

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