Tagipmet™

(Sitagliptin + Metformin HCl)

Highnoon

COMPOSITION

Tagipmet 50mg/500mg Tablet: Each film-coated tablet contains:
Sitagliptin (as phosphate monohydrate) 50mg
Metformin HCl 500mg

Tagipmet 50mg/1000mg Tablet: Each film-coated tablet contains:
Sitagliptin (as phosphate monohydrate) 50mg
Metformin HCl 1000mg

DESCRIPTION

Tagipmet tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: sitagliptin and metformin hydrochloride. Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme, while Metformin is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

MECHANISM OF ACTION

Sitagliptin

Sitagliptin inhibits dipeptidyl peptidase-4 (DPP-4), an enzyme responsible for degradation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). 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. 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 Hydrochloride

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, 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. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

PHARMACOKINETICS

Sitagliptin is absorbed from the gastrointestinal tract, with a peak plasma concentrations occurring about 1 to 4 hours after an oral dose, and bioavailability of about 87%. Because co-administration of a high-fat meal with Sitagliptin had no effect on the pharmacokinetics, Sitagliptin may be administered with or without food. It undergoes minimal metabolism, mainly by the cytochrome P450 isoenzymes CYP3A4, and to a lesser extent by CYP2C8. About 79% of the dose excreted unchanged in the urine. Renal excretion of Sitagliptin involves active tubular secretions; it is a substrate for organic anion transporter-3 and P-glycoprotein. Its terminal half-life is about 12 hours.

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500mg dose is reported to be about 50 to 60%, although this is reduced somewhat if taken with food. Protein binding in plasma is negligible. Metformin is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hour. Metformin crosses the placenta and is distributed into the breast milk in small amounts.

INDICATIONS

- It 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.
- It should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

DOSAGE AND ADMINISTRATION

The dosage 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. Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.

It should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin. It must not be split or divided before swallowing. The starting dose should be based on the patient's current regimen and should be given twice daily with meals. The recommended starting dose in patients not currently treated with metformin is 50 mg Sitagliptin / 500 mg metformin hydrochloride twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin. The starting dose in patients already treated with metformin should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of metformin already being taken. For patients taking metformin 850 mg twice daily, the recommended starting dose is 50 mg Sitagliptin / 1000 mg metformin hydrochloride twice daily.

Co-administration of this combination (Sitagliptin & Metformin Hydrochloride) 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.

Recommendation for use in Renal impairment

- Assess the renal function prior to initiation of this combination (Sitagliptin & Metformin Hydrochloride) and periodically thereafter. This combination (Sitagliptin & Metformin Hydrochloride) in contraindicated in patients with an estimated glomerular filtration rate (GFR) is below 30mL/min/1.73m². Discontinue it if the patient eGFR later falls below 30mL/min/1.73m². Initiation of this combination (Sitagliptin & Metfromin Hydrochloride) in patients with eGFR between 30 and 45mL/min/1.73m² is not recommended. In patients taking this combination (Sitagliptin & Metformin Hydrochloride) where eGFR later falls below 45mL/min/1.73m² assess the benefit risk of continuing therapy and limit dose of Sitagliptin compaired to 50mg once daily.

CONTRAINDICATIONS

Sitagliptin and Metformin Hydrochloride combination is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m²)
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to this combination (Sitagliptin and Metformin Hydrochloride) or any of its components such as anaphylaxis or angioedema.
- Hypersensitivity to metformin hydrochloride.

ADVERSE EFFECTS

The reported adverse effects include headache, lactic acidosis, heart failure, diarrhoea, upper respiratory tract infections, abdominal pain, nausea, vomiting, nasopharyngitis, peripheral oedema, hypoglycemia, flatulence, abdominal discomfort, indigestion, asthenia and a decrease to subnormal levels of previously normal serum vitamin B12 levels, a small increase in white blood cell count (WBC) was observed due to an increase in neutrophils, 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, myalgia, pain in extremity, back pain; pruritus, rhabdimyolysis, cholestatic, hepatocellular, and mixed hepatocellular liver injury.

DRUG INTERACTION

- Cationic drugs; Careful patient monitoring and dose adjustment of this combination (Sitagliptin & Metforim Hydrochloride) and/or the interfering drug is recommended in patients who are taking organic cationic transporter (e.g., cimetidine, amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin), multidrug and toxin extrusion 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.
- Carbonic anhydrase inhibitors; Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with this combination (Sitagliptin & Metforim Hydrochloride) as the risk of lactic acidosis may increase. Consider more frequent monitoring of these patients.
- Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving this combination (Sitagliptin & Metforim Hydrochloride).
- 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. When such drugs are administered to a patient receiving this combination (Sitagliptin & Metforim Hydrochloride) the patient should be closely observed to maintain adequate glycemic control.
- Coadministration of this combination (Sitagliptin & Metforim Hydrochloride) 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.
- Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin is recommended.

WARNINGS AND PRECAUTIONS

- Driving: Diabetes Mellitus, its complications and the medications used to treat it, may affect a patient's' ability to drive safely.
- Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
- There have been reported cases of metformin-associated lactic acidosis, including fatal cases. These accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate/pyruvate ratio; metformin plasma levels were generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk. If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of this combination (Sitagliptin & Metformin Hydrochloride) prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery. Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue It and report these symptoms to their healthcare provider.
- Metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Care should be taken in patients with renal impairment; renal function should be monitored throughout the therapy. Before initiating this combination (Sitagliptin & Metformin Hydrochloride) obtain an estimated glomerular filtration rate (eGFR).It is contraindicated in patients with an eGFR below 30mL/min/1.73 m² this combination (Sitagliptin & Metformin Hydrochloride) is not recommended in patients with an eGFR between 30 and < 45 mL/min /1.73 m² because these patients require a lower dosage of sitagliptin than what is available in the fixed combination. Obtain an eGFR at least annually in all patients taking this combination (Sitagliptin & Metformin Hydrochloride).
- The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.
- The concomitant use of this combination (Sitagliptin & Metformin Hydrochloride) 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. Concomitant medications that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion.
- Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. This combination (Sitagliptin & Metformin Hydrochloride) should be temporarily discontinued while patients have restricted food and fluid intake.
- Conditions associated with hypoxia, such as acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue this combination (Sitagliptin & Metformin Hydrochloride).
- Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. It should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.
- Alcohol is known to potentiate the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving It.
- 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 this combination (Sitagliptin & Metformin Hydrochloride) at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73m²; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart it if renal function is stable.
- A decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed. This decrease is possibly due to interference with B12 absorption from the B12-intrinsic factor complex. Measurement of hematologic parameters on an annual basis is advised in patients on this combination (Sitagliptin & Metformin Hydrochloride) and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate Vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B12 levels. In these patients, routine serum Vitamin B12 measurements at two-to three-year intervals may be useful.
- There have been reported cases of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking metformin/sitagliptin. Patients should be observed carefully for any sign and symptoms of pancreatitis. If pancreatitis is suspected, It should promptly discontinue and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Sitagliptin.
- Use with medications known to cause hypoglycemia.
- When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold this combination (Sitagliptin & Metformin Hydrochloride) and temporarily administer insulin. It may be reinstituted after the acute episode is resolved.
- There have been no clinical studies establishing conclusive evidence of macro vascular risk reduction with this combination (Sitagliptin & Metformin Hydrochloride) or any other anti-diabetic drug.
- Serious Hypersensitivity reactions (these reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome) and symptoms of allergic reactions (including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking Sitagliptin and seek medical advice promptly. If a hypersensitivity reaction is suspected, discontinue Sitagliptin, assess for other potential causes for the event, and institute alternative treatment for diabetes. Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Sitagliptin.
- Reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.
- Bullous Pemphigoid; cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. Tell patients to report development of blisters or erosions while receiving Sitagliptin. If bullous pemphigoid is suspected, it should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.
- These have been reports of worsening renal function including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with this combination (Sitagliptin & Metforfin Hydrochloride) and at least annually thereafter, renal function should be assessed. more frequently and discontinued if evidence of renal impairment is present. It is contraindicated in patients with severe renal impairment.
- An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed. Consider the risk and benefits of this combination (Sitagliptin & Metformin Hydrochloride) prior to initiating treatment in patients at risk of heart failure, such as those with a prior history of heart failure and history of renal impairment, and observe these patients for sign and symptoms of heart failure during therapy. Advice patients the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops evaluate and manage to current standards of care and consider discontinuation of this combination.

USED IN SPECIAL POPULATION

Pregnancy Category B

There are no adequate and well controlled studies in pregnant women with this combination (Sitagliptin & Metformin Hydrochloride) or its individual components. This drug should be used during pregnancy only if clearly needed.

Nursing Women

It is not known whether this combination (Sitagliptin & Metformin Hydrochloride) or its components are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when it is administered to a nursing woman.

Paediatric use

Safety and effectiveness of this combination (Sitagliptin & Metformin Hydrochloride) in paediatric patients under 18 years of age has not been established.

Geriatric Use

This combination (Sitagliptin & Metformin Hydrochloride) is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly, and it may be useful to assess renal function in these patients prior to initiating dosing and more frequently.

OVERDOSAGE

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.

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. 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.

DOSAGE AND INSTRUCTIONS

To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION

Tagipmet 50mg/500mg Film-coated Tablets:
Alu. Alu. Blister Pack of 2 x 7's.

Tagipmet 50mg/1000mg Film-coated Tablets:
Alu. Alu. Blister Pack of 2 x 7's.

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