90 mm

386 mm

Jentin met™

(Sitagliptin/Metformin HCl Ph. Eur.)

Tablets

WARNING
LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure.

The onset is often subtile, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. If acidosis is suspected, it should be discontinued and the patient hospitalized immediately.

Composition:
Jentin met 50mg/500mg:
Each film-coated tablet contains
Sitagliptin Phosphate Monohydrate eq. to
Sitagliptin..... 50 mg
Metformin HCl Ph. Eur 500mg

Jentin met 50mg/1000mg:
Each film-coated tablet contains
Sitagliptin Phosphate Monohydrate eq. to
Sitagliptin..... 50 mg
Metformin HCl Ph. Eur 1000mg

DRUG DESCRIPTION
Sitagliptin / metformin HCl tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: sitagliptin and metformin hydrochloride.

CLINICAL PHARMACOLOGY
Mechanism of Action
Sitagliptin / metformin HCl combines two anti hyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: 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 is believed to exert 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 an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances and do not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacodynamics
Sitagliptin
General
In patients with type 2 diabetes, administration of sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Sitagliptin and Metformin hydrochloride Co-administration
Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear what these findings mean for changes in glycemic control in patients with type 2 diabetes.

Pharmacokinetics
Sitagliptin / metformin, 50 mg/500 mg and 50 mg/1000 mg combination tablets are bioequivalent to co-administration of corresponding doses of sitagliptin and metformin hydrochloride as individual tablets.

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 hydrochloride
The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%. 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 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
The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. 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. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism
Sitagliptin
Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. Following a 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) nor biliary excretion.

Excretion
Sitagliptin
Following administration of an oral [^{14}C] sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. 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. Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Metformin Hydrochloride
Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin 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. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

INDICATIONS:
Sitagliptin / metformin 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. Sitagliptin / metformin 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 sitagliptin / metformin HCl.

DOSAGE AND ADMINISTRATION
Recommended Dosing
The dosage of (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 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. Sitagliptin / metformin should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin. The starting dose of Sitagliptin / metformin should be based on the patient's current regimen. Sitagliptin / metformin should be given twice daily with meals. The following doses are available:
50 mg sitagliptin/500 mg metformin hydrochloride
50 mg sitagliptin/1000 mg metformin hydrochloride.
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 of (sitagliptin/metformin HCl) is 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily.

PRECAUTIONS
Lactic Acidosis
Metformin Hydrochloride
Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with sitagliptin / metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (> 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels > 5 µg/mL are generally found.

Pancreatitis
There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin / metformin. After initiation of sitagliptin / metformin, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, sitagliptin / metformin should promptly be discontinued 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 / metformin.

Impaired Hepatic Function
Since impaired hepatic function has been associated with some cases of lactic acidosis, sitagliptin / metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Assessment of Renal Function
Metformin and sitagliptin are known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive sitagliptin / metformin. In the elderly, sitagliptin / metformin should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging can be associated with reduced renal function.

Vitamin B12 Levels
Measurement of hematologic parameters on an annual basis is advised in patients on sitagliptin / metformin and any apparent abnormalities should be appropriately investigated and managed.

Pregnancy
Pregnancy Category B:
There are no adequate and well-controlled studies in pregnant women with sitagliptin / metformin or its individual components; therefore, the safety of sitagliptin / metformin in pregnant women is not known. Sitagliptin / metformin should be used during pregnancy only if clearly needed.
Nursing Mothers
No studies in lactating animals have been conducted with the combined components of sitagliptin / metformin. Because many drugs are excreted in human milk, caution should be exercised when sitagliptin / metformin is administered to a nursing woman.
Pediatric Use
Safety and effectiveness of sitagliptin / metformin in pediatric patients under 18 years have not been established.
Geriatric Use
Because sitagliptin and metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, sitagliptin / metformin should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function.

SIDE EFFECTS:
Nausea, vomiting, stomach upset, diarrhea, headache, weakness, or a metallic taste in the mouth may occur. Stomach symptoms that occur after the first days of treatment may be signs of lactic acidosis. This medication does not usually cause low blood sugar (hypoglycemia). Low blood sugar may occur if this drug is prescribed with other anti-diabetic medications.
Symptoms of low blood sugar include sudden sweating, shaking, fast heartbeat, hunger, blurred vision, dizziness, or tingling hands/feet. It is a good habit to carry glucose tablets or gel to treat low blood sugar. Symptoms of high blood sugar (hyperglycemia) include thirst, increased urination, confusion, drowsiness, flushing, rapid breathing, and fruity breath odor.
A very serious allergic reaction to this drug is rare. However, medical help is advised against any of the following symptoms of a serious allergic reaction: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

OVERDOSE
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 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.

CONTRAINDICATIONS:
Sitagliptin / metformin is contraindicated in patients with:
• Renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
• Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
• History of a serious hypersensitivity reaction to sitagliptin / metformin or sitagliptin (one of the components of Jentin met), such as anaphylaxis or angioedema.
Sitagliptin / metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

HOW SUPPLIED
Jentin met 50mg/500mg tablets: are available in alu-alu blister pack of 14's & 28's (Blister of 7 Tablets).

Jentin met 50mg/1000mg tablets: are available in alu-alu blister pack of 14's & 28's (Blister of 7 Tablets).

Instructions:
To be sold on prescription of a registered medical practitioner only.
Protect from moisture, freezing, excessive heat and sunlight.
Store below 30ºC.
Keep out of the reach of children.

Mfg. Searle Specs.
SEARLE
Manufactured by:
The Searle Company Limited,
F-319, S.I.T.E., Karachi-Pakistan.
1565221114

PIL Code 102013
REV Code 082016

THE *SEARLE* COMPANY LIMITED

APPROVED

Product Name: Jentin Met
Artwork: Leaflet (SriLanka)
Creation Date: 02-08-2016
Revision Date: 31-11-2016
Revision Number: 4th
Size:(386x90)mm
Color:
Black

DEPARTMENT	NAME	SIGNATURE
Marketing		
Medical		
Regulatory		
QC		
Production		
B.D (Business Development)		