Inosita® Plus XR

[SITAGLIPTIN + METFORMIN HCl EXTENDED RELEASE]

اِنوسیٹا پلس ایکس آر

COMPOSITION

Inosita Plus XR 50/500:
Each tablet contains 64.25 mg Sitagliptin phosphate (equivalent to 50 mg Sitagliptin) and 500 mg Metformin hydrochloride extended-release.

Inosita Plus XR 50/1000:
Each tablet contains 64.25 mg Sitagliptin phosphate (equivalent to 50 mg Sitagliptin) and 1000 mg Metformin hydrochloride extended-release.

Inosita Plus XR 100/1000:
Each tablet contains 128.50 mg Sitagliptin phosphate (equivalent to 100 mg Sitagliptin) and 1000 mg Metformin hydrochloride extended-release.
(As per innovator's specs.)

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 impairment, renal impairment and acute congestive heart failure. The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. If acidosis is suspected, Sitagliptin and Metformin extended-release tablets should be discontinued and the patient hospitalized immediately. Dialysis is often recommended. See WARNINGS AND PRECAUTIONS

DESCRIPTION

Inosita Plus XR tablets contain two oral antidiabetic medications used in the management of type 2 diabetes: Sitagliptin and Metformin hydrochloride extended-release.

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-trifluoro-phenyl)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 $C_{16}H_{15}F_6N_5O{\bullet}H_3PO_4{\bullet}H_2O$ and a molecular weight of 523.32.

Metformin hydrochloride
Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide anti-diabetic drug with a molecular formula of $C_4H_{11}N_5{\bullet}HCl$ and a molecular weight of 165.63.

CLINICAL PHARMACOLOGY

Mechanism of Action
This product combines two anti-diabetic medications with complementary mechanisms of action to improve glycemic control in adults with type 2 diabetes: sitagliptin, a dipeptidyl peptidase-4 (DPP4) 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; thereby increasing the concentrations 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, 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 or healthy patients 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.

Pharmacodynamcis

Sitagliptin
In patients with type 2 diabetes, administration of sitagliptin lead to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP -4 inhibition results 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 is associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal. Co administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increases active GIP concentrations.

Pharmacokinetics

Absorption
After administration of Sitagliptin/Metformin extended release tablets with a high-fat breakfast, the AUC for sitagliptin is not altered. The mean Cmax is decreased by 17%, although the median Tmax remains unchanged relative to the fasted state. Whereas, the AUC for metformin increases to 62%, the Cmax for metformin decreases by 9%, and the median Tmax for metformin occurs 2 hours later relative to the fasted state.

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

Distribution

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

Metformin
The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averages 654 ± 358 L. Metformin is negligibly bound to plasma proteins. 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.

Metabolism

Sitagliptin
Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. Six metabolites of Sitagliptin are known to exist at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. The primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8.

Metformin hydrochloride
Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. No data is available on the metabolism of extended-release metformin tablets.

Elimination

Sitagliptin
The apparent terminal (half-life) $t_{1/2}$ following a 100-mg oral dose of sitagliptin is approximately 12.4 hours and renal clearance is 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. 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, does 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

INOSITA PLUS XR (Sitagliptin/Metformin extended release) tablets are 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.

Limitations of Use
• Sitagliptin/Metformin extended release tablets should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
• No data is available for the use of Sitagliptin/Metformin extended release 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 extended release formulation of Sitagliptin/Metformin.

DOSAGE AND ADMINISTRATION

Adult dosage
The dose of Inosita Plus 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. Initial combination therapy or maintenance of combination therapy should be individualized and is at the discretion of the health care provider.
• In patients not currently treated with metformin, the recommended total daily starting dose of Inosita Plus XR should be equivalent to 100 mg Sitagliptin and 1000 mg Metformin 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 of metformin i.e. 2000 mg
• In patients already treated with metformin, the recommended total daily starting dose of Inosita Plus XR is 100 mg Sitagliptin and the previously prescribed daily dose of Metformin.
• For patients taking metformin immediate-release 850 mg twice daily or 1000 mg twice daily, the recommended starting dose of Inosita Plus XR is two 50 mg Sitagliptin/1000 mg metformin extended-release tablets taken together once daily.
• Maintain the same total daily dose of Sitagliptin and Metformin when changing between Sitagliptin and Metformin immediate-release and Sitagliptin/Metformin extended release (Inosita Plus XR) tablets. 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 doses of Sitagliptin and Metformin.

Dosing considerations in special populations

Renal Impairment
Initiation of Sitagliptin/Metformin XR in patients with a creatinine clearance between 30 and 45 mL/min is not recommended. In patients taking Sitagliptin/Metformin XR whose creatinine clearance later falls below 45 mL/min, assess the benefit-risk ratio of continuing therapy and limit dose of the Sitagliptin component to 50 mg once daily.

Sitagliptin/Metformin XR is contraindicated in patients with an estimated creatinine clearance below 30 mL/min. Discontinue the drug if patient's creatinine clearance falls below 30 mL/min

Administration requirements
Inosita Plus XR tablets should be administered with food to reduce the gastrointestinal side effects associated with the metformin component. Inosita Plus XR tablets should be given once daily with a meal preferably in the evening. Inosita Plus XR tablets should be swallowed whole. The tablets must not be split, crushed, or chewed before swallowing.

CONTRAINDICATIONS

• Severe Renal impairment (creatinine clearance below 30 mL/min).
• Hypersensitivity to sitagliptin or metformin hydrochloride.
• Acute or chronic metabolic acidosis, including diabetic ketoacidosis coma. Diabetic ketoacidosis should be treated with insulin.
• Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock
• Acute conditions with the potential to alter renal function such as dehydration, severe infection, shock, intravascular administration of iodinated contrast agents
• Hepatic impairment.
• Acute alcohol intoxication, alcoholism

WARNING AND 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 XR. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis. The risk increases with conditions including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment and acute congestive heart failure, concomitant use of drugs impairing renal function, prolonged fasting and advanced age can precipitate metformin induced lactic acidosis. Use of topiramate, a carbonic anhydrase inhibitor may frequently cause dose-dependent metabolic acidosis and may exacerbate the risk of metformin-induced lactic acidosis.
The risk may be reduced significantly by regular monitoring of renal function (esp. in elderly patients) and by use of the minimum effective dose of metformin. See **Dosing considerations in special populations** for lactic acidosis risk prevention in patients with renal impairment. Metformin should be promptly withheld in the presence of conditions associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin is not recommended in hepatic disease. Patients should be cautioned against excessive alcohol intake, when taking metformin, since alcohol potentiates the effects of metformin on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radio-contrast diagnostic test and for any surgical procedure. Concomitant use of drugs decreasing renal function such as antihypertensives, diuretics and NSAIDs should be implemented with caution with metformin; alongside regular monitoring of renal function.

Lactic acidosis is characterized by elevated blood lactate concentrations (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Hypothermia, hypotension, and resistant bradyarrhythmias may occur with more marked acidosis.
Patients should be educated to promptly report these symptoms to their physician. If present, Sitagliptin/Metformin XR should be withdrawn until lactic acidosis is ruled out. Serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Lactic acidosis is a medical emergency that must be treated in a hospital setting. The drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin which often results in prompt reversal of symptoms and recovery.

Pancreatitis
Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis may occur in patients taking sitagliptin with or without metformin. After initiation of Sitagliptin/Metformin XR, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, the drug 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 XR.

Severe and disabling arthralgia
Severe and disabling arthralgia may occur in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy may vary from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue Sitagliptin/Metformin XR, if appropriate

Impaired Hepatic Function
Since impaired hepatic function has been associated with some cases of lactic acidosis, Sitagliptin/Metformin XR generally be avoided in patients with clinical or laboratory evidence of hepatic disease. See USE IN SPECIAL POPULATIONS

Assessment of Renal Function
Metformin and Sitagliptin are substantially excreted by the kidney.
The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of

renal function. Therefore, Sitagliptin/Metformin XR is contraindicated in patients with severe renal impairment having creatinine clearance below 30 mL/min.
There have been reports of worsening renal function in patients taking Sitagliptin with or without metformin, including acute renal failure, sometimes requiring dialysis. Before initiation of Sitagliptin/Metformin XR and at least annually thereafter, renal function should be assessed. In patients in whom worsening of renal dysfunction is anticipated (e.g., elderly), renal function should be assessed more frequently and Sitagliptin/Metformin XR discontinued, if evidence of renal impairment is present.

Vitamin B12 Levels
A decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, may occur in with patients treated with Metformin. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on Sitagliptin/Metformin XR 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 sub-normal Vitamin B12 levels. In these patients, routine serum Vitamin B12 measurements at two-to three-year intervals may be useful.

Alcohol Intake
Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving Sitagliptin/Metformin XR Metformin XR+Sitagliptin.

Surgical Procedures
Use of Sitagliptin/Metformin XR should be temporarily suspended 48 hours before for any surgical procedure with general, spinal or epidural anesthesia (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted earlier than 48 hours afterwards and until the patient's oral intake has resumed and renal function has been evaluated as normal.

Intravascular Iodinated Contrast Materials
Intravascular contrast studies with iodinated materials lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, Sitagliptin/Metformin XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been reevaluated and found to be normal.

Hypoxic States
Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause pre-renal azotemia. When such events occur in patients on Sitagliptin/Metformin XR therapy, the drug should be promptly discontinued.

Heart Failure
An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease (in certain cardiovascular outcomes studies) for two other members of the DPP-4 inhibitor class.
Consider the risks and benefits of Sitagliptin/Metformin XR 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 XR.

Loss of Control of Blood Glucose
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 Sitagliptin/Metformin XR and temporarily administer insulin. Sitagliptin/Metformin XR may be reinstituted after the acute episode is resolved.

Hypoglycemia
Patients taking Sitagliptin/Metformin XR 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. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β-blockers.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes
A patient with type 2 diabetes, previously well controlled on Sitagliptin /metformin who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness); should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, sitagliptin /metformin must be stopped immediately and other appropriate corrective measures initiated

Hypersensitivity Reactions
Serious hypersensitivity reactions may occur in patients treated with Sitagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset could be within the first 3 months after initiation of treatment with Sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue Sitagliptin/Metformin XR, assess for other potential causes for the event, and institute alternative treatment for diabetes. Exercise caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with Sitagliptin/Metformin XR.

Bullous Pemphigoid
Reports of bullous pemphigoid requiring hospitalization have been noticed with DPP-4 inhibitor use. Patients typically recover with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Patients should be asked to report development of blisters or erosions while receiving Sitagliptin/Metformin XR. If bullous pemphigoid is suspected, Sitagliptin/Metformin XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Macrovascular Outcomes
There is no data available establishing conclusive evidence of macro vascular risk reduction with Sitagliptin/Metformin XR or other DPP-IV inhibitors or biguanides.

Effects on ability to drive and use machines
Sitagliptin/Metformin XR has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence has been reported with Sitagliptin. In addition, patients should be alerted to the risk of hypoglycemia when sitagliptin /metformin XR is used in combination with a sulphonylurea or with insulin. Hypoglycemia symptoms may impair the ability of an individual to drive or operate machines.

ADVERSE REACTIONS
Immune system disorders:
Not known: Hypersensitivity reactions including anaphylaxis.
Skin and Subcutaneous tissue disorders:
Uncommon: Pruritus
Not known: Angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome, bullous pemphigoid
Metabolism and nutrition disorders
Common: Hypoglycemia
Respiratory, thoracic and mediastinal disorders
Common: Upper respiratory tract infection,
Not known: Interstitial lung disease
Hepatobiliary Disorders:
Not known: Hepatic enzyme elevations, cholestatic / hepatocellular / mixed hepatocellular liver injury
Renal and Urinary Disorders:
Not known: Worsening renal function, including acute renal failure (sometimes requiring dialysis)
Gastrointestinal Disorders:
Not known: Acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis,
Common: Nausea, vomiting, flatulence
Uncommon: Constipation, diarrhea, upper abdominal pain
Nervous System Disorders:
Common: Headache
Uncommon: Somnolence
Musculoskeletal and Connective tissue disorders:
Not known: Arthralgia, myalgia, pain in extremity, back pain, arthropathy

DRUG INTERACTIONS

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 Sitagliptin/Metformin XR, as the risk of lactic acidosis may increase.

Cationic Drugs
Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, cimetidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin 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 XR and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system. Multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir may also be implicated in these kind of interactions.

Drugs causing hyperglycemia
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 Sitagliptin/Metformin XR, the patient should be closely observed to maintain adequate glycemic control and dose adjustment of the drugs in anti-hyperglycemic regimen may be needed.

Iodinated contrast agents
The intravascular administration of iodinated contrast agents in radiological tests can lead to renal failure which has been associated with lactic acidosis in patients receiving metformin. Therefore, treatment with Sitagliptin/Metformin XR 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.

ACE inhibitors
ACE-inhibitors may decrease the blood glucose levels. If necessary, the dose of Sitagliptin/Metformin XR should be adjusted to prevent undesirable hypoglycemia.

Potent CYP3A4 Inhibitors
Primary enzyme responsible for the limited metabolism of Sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism via CYP3A4, plays only a small role in the clearance of sitagliptin while it may play a more significant role in elimination of sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD). Potent CYP3A4 inhibitors (i.e.ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD. The effects of potent CYP3A4 inhibitors in the setting of renal impairment have not been assessed

Digoxin
Sitagliptin has a small effect on plasma digoxin concentrations. No dose adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when Sitagliptin containing preparations and digoxin are administered concomitantly.

Alcohol
Consumption of alcohol and medications containing alcohol should be avoided with metformin as this may result in increased risk of lactic acidosis particularly in the case of fasting, malnutrition or hepatic insufficiency.

USE IN SPECIAL POPULATIONS

Pregnancy
US FDA Pregnancy Category B: Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or fetal development, parturition or postnatal development while limited reproductive toxicity was observed only at high doses of sitagliptin.
There are no adequate and well-controlled studies in pregnant women with Sitagliptin/Metformin XR or its individual components; therefore, the safety of Sitagliptin/Metformin XR in pregnant women is not known. Sitagliptin/Metformin XR should be used during pregnancy, only if clearly needed. During pregnancy anti-hyperglycemic therapy may be switched to insulin.

Nursing mothers
Metformin is excreted in human milk in small amounts. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Sitagliptin/ metformin is administered to a nursing woman. Because many drugs are excreted in human milk, caution should be exercised when Sitagliptin/Metformin XR is administered to a nursing woman.

Pediatrics
Safety and effectiveness of Sitagliptin/Metformin XR in pediatric patients under 18 years have not been established.

Elderly
Because sitagliptin and metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, Sitagliptin/Metformin XR 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. Low starting doses are recommended in elderly

Renal impairment
Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Initiation of Sitagliptin/Metformin XR in patients with a creatinine clearance between 30 and 45 mL/min is not recommended. In patients taking Sitagliptin/Metformin XR whose creatinine clearance later falls below 45 mL/min, assess the benefit-risk ratio of continuing therapy and limit dose of the Sitagliptin component to 50 mg once daily.

Sitagliptin/Metformin XR is contraindicated in patients with an estimated creatinine clearance below 30 mL/min. Discontinue the drug if patient's creatinine clearance falls below 30 mL/min

Hepatic impairment
In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and Cmax of immediate-release sitagliptin increased approximately 21% and 13% with administration of a single 100-mg dose of sitagliptin. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score >9).

No data is available in patients with hepatic impairment. Impaired hepatic function has been associated with some cases of lactic acidosis. Therefore, Sitagliptin/Metformin XR must not be used in patients with hepatic disease.

OVER DOSAGE

Sitagliptin
No dose-related clinical adverse reactions have been observed with sitagliptin with doses of up to 400 mg per day for periods of up to 28 days. 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. Approximately 13.5% of the dose may be removed over a 3-to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if Sitagliptin is dialyzable by peritoneal dialysis.

Metformin hydrochloride
After ingestion of amounts greater than 50 grams, overdose of metformin hydrochloride has occurred. Hypoglycemia is known to occur but no causal association with metformin has been established. A large overdose of metformin (or co-existing risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is hemodialysis. Approximately 13.5 % of the dose can be removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered, if clinically appropriate. 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 over dosage is suspected.

PRESENTATION
Inosita Plus XR 50/500: Pack of 14 Tablets.
Inosita Plus XR 50/1000: Pack of 14 Tablets.
Inosita Plus XR 100/1000: Pack of 14 Tablets.

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INSTRUCTIONS

Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email us at reports@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

ہدایات:
ڈاکٹری ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے لئے پرچی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ، 30°C سے کم درجہ حرارت پر رکھیں۔
دوا کے ممکنہ منفی اثرات کے متعلق reports@pharmevo.biz

پر مطلع کریں۔
ہماری ادویات کی مزید معلومات کے لئے فارماسسٹ کی
ہیلپ لائن نمبر 0800-82222 پر کال کریں۔
پیر تا جمعہ صبح 9:00 بجے تا شام 6:00 بجے
یا ہمیں pharmassist@pharmevo.biz پر ای میل کریں

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