Inosita® Plus انوسیٹا پلس

[SITAGLIPTIN + METFORMIN HCl]

COMPOSITION

Inosita® Plus 50/500 mg Tablet
Each film coated tablet contains:
Sitagliptin....50mg (as phosphate monohydrate) USP /Metformin HCl USP....500mg
Inosita® Plus 50/850mg Tablet
Each film coated tablet contains:
Sitagliptin....50mg (as phosphate monohydrate) USP/Metformin HCl USP.....850mg
Inosita® Plus 50/1000mg Tablet
Each film coated tablet contains:
Sitagliptin...50mg (as phosphate monohydrate) USP/Metformin HCl USP....1000mg
(PharmEvo 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 is often subtle, accompanied by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. If acidosis is suspected, Sitagliptin/metformin should be discontinued and the patient hospitalized immediately for appropriate treatment.

DESCRIPTION

Inosita Plus tablets contain two oral hypoglycemic drugs used in the management of Type II diabetes: Sitagliptin phosphate monohydrate and Metformin hydrochloride.
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-trifluorophenyl)butyl]-5,6,7,8−tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate with a molecular formula of C16H15F6N5O•H3PO4•H2O.
Metformin hydrochloride belongs to Biguanide class which is chemically designated as (N, N-dimethylimidodicarbonimidic diamide hydrochloride) with a molecular formula of C4H11N5•HCl.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Mechanism of Action
Inosita Plus combines two antihyperglycaemic drugs with complementary mechanisms of action to improve glycemic control in patients with Type II diabetes: sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor and metformin hydrochloride, a member of the biguanide class.

Sitagliptin
Sitagliptin is a DPP-4 inhibitor, which exerts its actions in patients with Type II diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact incretin 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. 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 improves glucose tolerance in patients with Type II 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 increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4). It also stimulates intracellular glycogen synthesis by acting on glycogen synthase.
Unlike sulfonylureas, metformin does not produce hypoglycemia (except in special circumstances) and does not cause hyper-insulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacokinetics

The pharmacokinetics of Sitagliptin and metformin combination tablets is comparable to co-administration of corresponding doses of sitagliptin and metformin as individual tablets.

Absorption

Sitagliptin
Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 μM•hr, Cmax was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.
Plasma AUC of sitagliptin increases in a dose-proportional manner.

Metformin hydrochloride
After an oral dose of metformin, Tmax is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30 %. After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 μg/mL. Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease 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
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranges between 63 – 276 L.

Metabolism

Sitagliptin
Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine. Following a [14C] sitagliptin oral dose, approximately 16% of the radioactivity is 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 have indicated that 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 nor biliary excretion.

Excretion

Sitagliptin
Following administration of an oral [14C] sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces (13%) or urine (87%) within one week of dosing. The apparent terminal t½ following a 100-mg oral dose of sitagliptin is approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The 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) and p-glycoprotein, which may also be involved in mediating the renal elimination 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 is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type II diabetes mellitus when treatment with both sitagliptin and metformin is appropriate.
• Inosita Plus is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or in those already taking separate tablets of sitagliptin and metformin.
• Inosita plus is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.
• Inosita plus is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.
• Inosita plus is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycemic control.

DOSAGE AND ADMINISTRATION

The dosage of Inosita plus 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. Inosita Plus should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin.

• For patients inadequately controlled on maximal tolerated dose of metformin monotherapy
For patients not adequately controlled on metformin alone, the usual starting dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken.

• For patients switching from co-administration of sitagliptin and metformin
For patients switching from co-administration of sitagliptin and metformin, Inosita plus should be initiated at the dose of sitagliptin and metformin already being taken.

• For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulphonylurea
The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Inosita plus is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia.

• For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a PPARγ agonist
The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken.

• For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin
The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Inosita plus is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycemia. All patients should continue their recommended diet with an adequate distribution of carbohydrate intake during the day.

Dosing consideration in special populations:

Patients with Renal impairment
No dose adjustment is needed for patients with mild renal impairment (creatinine clearance [CrCl] ≥ 60 mL/min). Inosita plus must not be used in patients with moderate or severe renal impairment (creatinine clearance < 60 mL/min).

Patients with Hepatic impairment
Inosita plus must not be used in patients with hepatic impairment.

Administration requirements
Inosita plus should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin. Inosita plus must not be split or divided before swallowing.

CONTRAINDICATIONS

• Moderate or severe Renal impairment creatinine clearance less than 60 ml/min), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, intravascular administration of iodinated contrast agents, severe dehydration, severe infection and septicemia.
• Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock
• Hepatic impairment.
• Acute alcohol intoxication, alcoholism.
• Acute or chronic metabolic acidosis including diabetic ketoacidosis, diabetic pre-coma. Diabetic ketoacidosis should be treated with insulin.
• Hypersensitivity to sitagliptin phosphate monohydrate or metformin HCl, such as anaphylaxis or angioedema.

WARNINGS AND PRECAUTIONS

Type I diabetes and diabetic ketoacidosis
Sitagliptin and metformin should not be used in patients with Type I diabetes and must not be used for the treatment of diabetic ketoacidosis.

Lactic acidosis
Lactic acidosis is a very rare, but serious, metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis with metformin have occurred mainly in diabetic patients with significant renal impairment (including both intrinsic renal disease and renal hypoperfusion), often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Other risk factors include significant tissue hypoperfusion and hypoxemia (such as unstable or acute congestive heart failure) as well as advanced age.
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. 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.
Lactic acidosis is characterized by malaise, myalgias, increasing somnolence, acidotic dyspnoea, abdominal pain, hypotension, bradyarrhythmias and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. Levels of lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate lactic acidosis and may be due to other factors, such as poorly controlled diabetes, obesity or vigorous physical activity. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).
If acidosis is suspected, treatment with the drug should be discontinued and the supportive treatment should be instituted promptly. Metformin is dialyzable and prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin which often results in prompt reversal of symptoms and recovery.

Pancreatitis
Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin (with or without supportive treatment), but very rare cases of necrotising or hemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, drug should be discontinued; if acute pancreatitis is confirmed, drug should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Renal function
Metformin and sitagliptin are known to be substantially excreted by the kidney. There have been post-marketing reports of worsening renal function with Sitaglitpin, including acute renal failure, sometimes requiring dialysis. Metformin-related lactic acidosis increases with the degree of impairment of renal function, therefore, serum creatinine concentrations should be determined regularly:

- Before initiation of therapy and at least once a year (in patients with normal renal function)
- at least two to four times a year in patients with mild renal impairment and in elderly patients.

Inosita Plus must not be used in patients with moderate to severe renal impairment. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with a non-steroidal anti-inflammatory drug (NSAID).

Hypoglycemia
Patients taking Inosita Plus 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

Impaired hepatic function
Impaired hepatic function has been associated with lactic acidosis, sitagliptin phosphate/metformin hydrochloride must not be used in hepatic impairment. See USE IN SPECIAL POPULATIONS

Vitamin B_{12} levels
Metformin use may lead to sub-normal levels of previously normal serum B12 levels possibly due to interference with B12 absorption from the B12-intrinsic factor complex; however it's very rarely associated with anemia and is 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 and any apparent abnormalities should be appropriately 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.

Alcohol Intake
Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving sitagliptin /metformin.

Surgery
Inosita plus contains metformin hydrochloride, the treatment should be discontinued 48 hours before elective surgery with general, spinal or epidural anesthesia. Treatment should not usually be resumed earlier than 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.

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.

Concomitant drugs affecting Renal Function or Metformin Disposition
Concomitant drugs 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 should be used with caution.

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 therapy, the drug should be promptly discontinued.

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 and temporarily administer insulin. Sitagliptin /metformin may be reinstituted after the acute episode is resolved.

Hypersensitivity reactions
Serious hypersensitivity reactions in patients treated with sitagliptin have been reported including anaphylaxis, angioedema, and exfoliative skin conditions such as Stevens-Johnson syndrome. Onset of these reactions occurred within the first three months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, Inosita Plus should be discontinued, other potential causes of the event should be assessed, and alternative treatment for diabetes should be instituted.

Severe and disabling arthralgia
There have been post-marketing 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 drug. Some patients may have 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 drug if appropriate.

Administration of iodinated contrast agents
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. Therefore, treatment 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

Effects on ability to drive and use machines
Sitagliptin/metformin 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 have been reported with sitagliptin. In addition, patients should be alerted to the risk of hypoglycaemia when sitagliptin /metformin 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 anaphylactic responses
Metabolism and nutrition disorders
Common: hypoglycemia
Nervous system disorders
Uncommon: Somnolence
Respiratory, thoracic and mediastinal disorders
Not known: interstitial lung disease
Gastrointestinal disorders
Uncommon: diarrhea, constipation, upper abdominal pain
Common: nausea, vomiting, flatulence
Not known: acute pancreatitis, fatal and non-fatal hemorrhagic and necrotizing pancreatitis
Skin and subcutaneous tissue disorders
Uncommon: pruritus
Not known: angioedema, rash, urticarial, cutaneous vasculitis, exfoliative skin conditions including Stevens-Johnson syndrome, bullous pemphigoid
Musculoskeletal and connective tissue disorders
Not known: arthralgia, myalgia, pain in extremity, back pain, arthropathy
Renal and urinary disorders
Not known: impaired renal function, acute renal failure

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 with metformin containing products such as Inosita Plus may induce metabolic acidosis. Use these drugs with caution in patients treated with sitagliptin/metformin, 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 and/or the interfering drug is recommended in patients who are taking cationic medications.

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, beta-2-agonists and isoniazid. When such drugs are administered to a patient receiving sitagliptin /metformin 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 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 Inosita Plus should be adjusted to prevent undesirable hypoglycemia.

Cyclosporin
Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of ciclosporin (a potent P-gp inhibitor) increased the AUC and Cmax of sitagliptin by approximately 29 % and 68 %, respectively. However, these changes in sitagliptin pharmacokinetics are not considered to be clinically meaningful and the renal clearance of sitagliptin is not meaningfully altered. Therefore, significant interactions would not be expected with other p-glycoprotein inhibitors.

Probenecid
OAT3 mediated transport of Sitagliptin is inhibited in vitro by Probenecid, although the risk of significant interaction is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluated in vivo.

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 phamacokinetics 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 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 foetal 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 or its individual components and it's safety in pregnant women is not known. Sitagliptin /metformin 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.

Pediatric use
Safety and effectiveness of sitagliptin /metformin in pediatric patients under 18 years have not been established.

Elderly use
Because sitagliptin and metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, Inosita Plus should be used with caution in elderly. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Monitoring of renal function is important to aid in prevention of metformin-associated lactic acidosis

Renal impairment
Patients with mild renal impairment do not have a clinically meaningful increase in the plasma concentration of sitagliptin as compared to patients with intact renal function. An approximately 2-fold increase in the plasma AUC of sitagliptin has been observed in patients with moderate renal impairment, and an approximately 4-fold increase in patients with severe renal impairment and ESRD on hemodialysis. When renal function is impaired, renal clearance of metformin is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Inosita Plus must not be used in patients with moderate or severe renal impairment (creatinine clearance < 60 mL/min). No dose adjustment is needed for patients with mild renal impairment (creatinine clearance [CrCl] equal to/greater than 60 mL/min).

Hepatic impairment
In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and Cmax of 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 pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment. Impaired hepatic function has been associated with some cases of lactic acidosis. Therefore, Inosita Plus (Sitagliptin/metformin) must not be used in patients with hepatic disease.

OVERDOSAGE

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 haemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis. In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastro-intestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

PRESENTATION
Inosita® Plus 50/500mg Tablets : 28's Tablets.
Inosita® Plus 50/850mg Tablets : 28's Tablets.
Inosita® Plus 50/1000mg Tablets : 28's Tablets.

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:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچّوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی 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۔

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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

Our dream, a healthier society

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