Inosita®

[SITAGLIPTIN USP]

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COMPOSITION

INOSITA 25 mg Tablet
Each film coated tablet contains:
Sitagliptin……..25 mg
(as phosphate monohydrate) USP
INOSITA 50 mg Tablet
Each film coated tablet contains:
Sitagliptin……..50 mg
(as phosphate monohydrate) USP
INOSITA 100 mg Tablet
Each film coated tablet contains:
Sitagliptin……..100 mg
(as phosphate monohydrate) USP
(USP Specs.)

DESCRIPTION
INOSITA Tablets contain sitagliptin phosphate, an orally-active inhibitor of the dipeptidyl peptidase¬4 (DPP-4) enzyme, used as an oral hypoglycemic agent in Type II diabetes mellitus. It is chemically described as 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. The molecular formula is $C_{16}H_{15}F_6N_5O•H_3PO_4•H_2O$

CLINICAL PHARMACOLOGY

Pharmacodynamics

Mechanism of Action
INOSITA (Sitagliptin) is an inhibitor of DPP-IV enzyme which is responsible for the inactivation of incretin hormones. Sitagliptin is believed to exert its actions in Type II Diabetes by increasing and prolonging the action of incretin hormones including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).
GLP-1 and 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.

In patients with type 2 diabetes with hyperglycemia, these changes in insulin and glucagon levels lead to lower hemoglobin A1c (HbA1c) and lower fasting and postprandial glucose concentrations.

Pharmacokinetics

Absorption
Following oral administration of a 100mg dose, Sitagliptin absorbs rapidly with peak plasma concentration occurring 1 to 4 hours post-dose. The absolute bioavailability of Sitagliptin is approximately 87%. Because co-administration of a high-fat meal with sitagliptin has no effect on the pharmacokinetics, Sitagliptin may be administered with or without food. Plasma AUC of Sitagliptin increases in a dose-proportional manner.

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

Metabolism
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 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.

Excretion
Following administration of an oral sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces (13 %) or urine (87 %) within one week of dosing. Sitagliptin accumulates only minimally with multiple doses.
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 be involved in the renal elimination of Sitagliptin.

Sitagliptin is primarily excreted unchanged in urine (approximately 79%), and metabolism is a minor pathway of elimination. The apparent terminal half-life t 1/2 following a 100mg oral dose of Sitagliptin is approximately 12.4 hours and renal clearance is approximately 350mL/min.

INDICATIONS

For adult patients with type 2 diabetes mellitus, INOSITA is indicated to improve glycemic control as an adjunct to diet and exercise:

Monotherapy
In patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

Dual oral therapy
In combination with metformin or with a sulfonylurea or with a PPAR agonist (i.e. thiazolidinedione) when the treatment with the single agent alone, with diet and exercise, does not provide adequate glycemic control

Triple oral therapy
In combination with metformin and a sulfonylurea or with metformin and a PPAR agonist (i.e. thiazolidinedione) when dual therapy with these agents, with diet and exercise, does not provide adequate glycemic control

Combination therapy with Insulin with or without metformin
Inosita is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycemic control.

Limitations of Use
Not suitable for use in type I diabetes mellitus or for the treatment of diabetic ketoacidosis.

DOSAGE AND ADMINISTRATION

The dose is 100 mg sitagliptin once daily. When used in combination with metformin and/or a PPARγ agonist, the dose of metformin and/or PPARγ agonist should be maintained, and Sitagliptin administered concomitantly.

When Sitagliptin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycemia.
If a dose of Sitagliptin is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

Dose adjustment and dosing considerations in Special populations

Renal Impairment
Dosage adjustment is recommended in patients with moderate or severe renal impairment and in patients with ESRD - End Stage Renal Disease.
For patients with mild renal impairment (creatinine clearance [ClCr] equal to or greater than 50ml/min and below 80ml/min) no dosage adjustment for Sitagliptin is required. For patients with moderate renal impairment (ClCr 30 to <50 mL/min), the dose of Sitagliptin is 50 mg once daily. For patients with severe renal impairment (ClCr <30 mL/min), or those with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, the dose of Sitagliptin is 25mg once daily. Sitagliptin may be administered without regard to the timing of hemodialysis.

Hepatic Impairment
No dose adjustment is required for mild to moderate hepatic impairment (Child Pugh score 5-9). There is no clinical experience in patients with severe hepatic impairment (Child Pugh score greater than 9).

Method of administration
Sitagliptin should be swallowed whole and tablets should not be split, crushed, or chewed before swallowing. Co administration of a high-fat meal with Sitagliptin had no effect on the pharmacokinetics; Sitagliptin may be administered with or without food.

CONTRAINDICATIONS

Hypersensitivity to Sitagliptin

WARNINGS AND PRECAUTIONS

Pancreatitis
There have been post-marketing reports of acute pancreatitis. After initiation of Sitagliptin, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, Sitagliptin should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of

pancreatitis while using Sitagliptin.

Severe and Disabling Arthralgia
Severe and disabling arthralgia (joint pain) has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug, if appropriate.

Hypoglycemia
When Sitagliptin is used in combination with a sulfonylurea or with insulin, there is an increased risk of hypoglycemia. Therefore a lower dose of sulfonylurea or insulin may be required.

Renal Impairment
Sitagliptin has NOT been found to be nephrotoxic in clinical trials. However, there have been post marketing reports of worsening renal function, including acute renal failure sometimes requiring dialysis. Assessment of renal function is recommended prior to initiating Sitagliptin and periodically thereafter. Dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with ESRD - End Stage Renal Disease.

Allergic and Hypersensitivity Reactions
There have been post-marketing reports of serious allergic and hypersensitivity reactions in patients treated with Sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, discontinuation of the drug should be considered.

Effects on ability to drive and use machines
Sitagliptin 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.
In addition, patients should be alerted to the risk of hypoglycemia when Sitagliptin is used in combination with a sulphonylurea or with insulin. Hypoglycemia symptoms such as weakness, confusion, loss of consciousness may impair the ability of patients to drive or use machines.

ADVERSE REACTIONS

Immune System disorders
Unknown frequency: Hypersensitivity reactions including anaphylactic responses
Metabolic & Nutrition disorders
Common: Hypoglycemia
Nervous System disorders
Common: Headache
Uncommon: Dizziness
Respiratory, Thoracic & Mediastinal disorders
Unknown frequency: Interstitial lung disease
Gastrointestinal disorders
Uncommon: Constipation
Unknown frequency: Vomiting, Acute Pancreatitis, Fatal & non-fatal Hemorrhagic and Necrotizing Pancreatitis
Skin and subcutaneous tissue disorders
Uncommon: Pruritus
Unknown frequency: Angioedema, Rash, Urticaria, Cutaneous Vasculitis, Exfoliative skin conditions including Stevens - Johnson syndrome, Bullous pemphigoid
Musculoskeletal and connective tissue disorders
Unknown frequency: Arthralgia, Myalgia, Back pain, Arthropathy
Renal & Urinary disorders:
Unknown frequency: Impaired renal function, acute renal failure

Some adverse reactions were reported more commonly in studies of combination use of Sitagliptin with other anti-diabetic drugs than in studies of Sitagliptin monotherapy. These include:

Hypoglycemia (frequency very common with the combination of sulphonylurea and metformin),
Influenza (common with insulin (with or without metformin),
Nausea and Vomiting (common with metformin),
Flatulence (common with metformin or pioglitazone),
Constipation (common with the combination of sulphonylurea and metformin),
Peripheral edema (common with pioglitazone or the combination of pioglitazone and metformin),
Somnolence and diarrhea (uncommon with metformin),
Dry mouth (uncommon with insulin (with or without metformin)

DRUG INTERACTIONS

Digoxin
Sitagliptin has a small effect on plasma digoxin concentrations. No dosage adjustment of digoxin or Sitagliptin is recommended. However, patients should be monitored for digoxin toxicity when Sitagliptin and digoxin are administered concomitantly.

USE IN SPECIAL POPULATIONS

Pregnancy
US FDA Pregnancy category B. The safety of Sitagliptin in pregnant women is not known. Sitagliptin should be avoided in pregnancy, unless clearly needed.

Nursing mothers
It is not known whether Sitagliptin is excreted in human milk. Caution should be exercised when administering Sitagliptin to nursing mothers.

Pediatrics
The safety and efficacy of sitagliptin in children and adolescents under 18 years of age have not been established.

Elderly
No dose adjustment is necessary based on age.

Renal impairment
Patients with mild renal impairment did not have a clinically meaningful increase in the plasma concentration of Sitagliptin. The plasma AUC of Sitagliptin increases approximately 2-fold in patients with moderate renal impairment, and an approximately 4-fold in patients with severe renal impairment and in patients with End Stage Renal Disease (ESRD) on hemodialysis.
Dosage adjustment is required which is based upon renal function, assessment of renal function is recommended prior to initiation of sitagliptin and periodically thereafter (See DOSAGE & ADMINISTRATION and WARNINGS & PRECAUTIONS)

Hepatic impairment
In patients with moderate hepatic insufficiency (Child-Pugh score 7-9), no clinically meaningful alternations in pharmacokinetics were noted.

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

No dose adjustment is necessary for patients with mild to moderate hepatic impairment. (See DOSAGE& ADMINISTRATION)

OVER DOSAGE

In the event of an overdose with INOSITA (Sitagliptin), 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 dictated by the patient's clinical status. Sitagliptin is modestly dialyzable. Approximately 13.5% of the dose can be removed over a 3 to 4 hour hemodialysis session starting 4 hours post-dose. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if Sitagliptin is dialyzable by peritoneal dialysis.

PRESENTATION

Inosita 25mg : Pack of 10 Tablets.
Inosita 50mg : Pack of 28 Tablets.
Inosita 100mg : Pack of 28 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

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ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کی جائے۔
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