22-03-2022
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Addition of Strength

ITAGLIP® Plus XR Tablet

(Sitagliptin Phosphate + Metformin HCl)

WARNING: LACTIC ACIDOSIS

Post marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio, and metformin plasma levels generally >5 mcg/mL.
Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.
Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information. If metformin-associated lactic acidosis is suspected, immediately discontinue and institute general supportive measures in a hospital setting. Prompt haemodialysis is recommended.

QUALITATIVE AND QUANTITATIVE COMPOSITION

ITAGLIP® Plus XR Tablet 50/500mg	ITAGLIP® Plus XR Tablet 50/1000mg	ITAGLIP® Plus XR Tablet 100/1000mg
Each film coated tablet contains:	Each film coated tablet contains:	Each film coated tablet contains:
Sitagliptin Phosphate Monohydrate USP eq. to Sitagliptin.....50mg (as Immediate Release Coating)	Sitagliptin Phosphate Monohydrate USP eq. to Sitagliptin.....50mg (as Immediate Release Coating)	Sitagliptin Phosphate Monohydrate USP eq. to Sitagliptin.....100mg (as Immediate Release Coating)
Metformin HCl BP...500mg (as Extended Release Core)	Metformin HCl BP...1000mg (as Extended Release Core)	Metformin HCl BP...1000mg (as Extended Release Core)

PHARMACEUTICAL FORM

Tablet

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS:

ITAGLIP® Plus XR tablet is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Limitations of Use: Sitagliptin/metformin extended release tablets should not be used in patients with type 1 diabetes mellitus. No data is available for the use of sitagliptin/metformin extended release in patients with a history of pancreatitis.

POSOLOGY AND METHOD OF ADMINISTRATION:

Adult dosage:

- Take ITAGLIP® Plus XR tablet orally once daily with a meal. Patients taking two ITAGLIP® Plus XR tablet should take the two tablets together once daily.
- Individualize the dosage of ITAGLIP® Plus XR tablet on the basis of the patient's current regimen, effectiveness, and tolerability.
- The maximum recommended daily dose is 100mg of sitagliptin and 2000mg of metformin hydrochloride (HCl) extended-release.
- The recommended starting dose in patients not currently treated with metformin is 100mg sitagliptin and 1000mg metformin HCl extended-release once 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 100mg sitagliptin and the previously prescribed dose of metformin.
- For patients taking metformin HCl immediate-release 850mg twice daily or 1000mg twice daily, the recommended starting dose of ITAGLIP® Plus XR is two 50mg sitagliptin and 1000mg metformin HCl extended-release tablets taken together once daily.
- Do not split, crush or chew tablet

Recommendations for Use in Renal Impairment:

- Assess renal function prior to initiation of sitagliptin/metformin extended release tablets and periodically thereafter.
- Sitagliptin/metformin extended release tablets is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30mL/min/1.73 m^2. Discontinue sitagliptin/metformin extended release tablets if the patient's eGFR later falls below 30 mL/min/1.73 m^2.
- Initiation of sitagliptin/metformin extended release tablets in patients with an eGFR between 30 and 45mL/min/1.73 m^2 is not recommended.
- In patients taking sitagliptin/metformin extended release tablets whose eGFR later falls below 45mL/min/1.73 m^2, assess the benefit risk of continuing therapy and limit dose of the sitagliptin component to 50mg once daily.

For Iodinated Contrast Imaging Procedures: Discontinue sitagliptin/metformin extended release tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart sitagliptin/metformin extended release tablets if renal function is stable
Paediatric population: No studies are performed in paediatric population under 18 years of age.
Geriatric population: No dose adjustment is recommended but monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly.

CONTRAINDICATIONS:

ITAGLIP® Plus XR tablet is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) ITAGLIP® Plus XR. Acute or chronic metabolic acidosis, including diabetic ketoacidosis.
- History of a serious hypersensitivity reaction to ITAGLIP® Plus XR, sitagliptin or metformin such as anaphylaxis or angioedema.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Lactic Acidosis: Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate/pyruvate ratio; metformin plasma levels were generally >5 mcg/mL. If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted.
Renal Impairment: Clinical recommendations based upon the patient's renal function include; contraindicated in patients with an eGFR less than 30 mL/min/1.73m^2.
Discontinue if the patient's eGFR later falls below 30 mL/min/1.73m^2.
Initiation is not recommended in patients with eGFR between 30 and 45 mL/min/1.73m^2. In patients whose eGFR later falls below 45 mL/min/1.73m^2, assess the benefit and risk of continuing therapy. Obtain an eGFR at least annually in all patients taking ITAGLIP® Plus XR tablet.
Drug Interactions: Consider more frequent monitoring of patients.
Age 65 or above: Assess renal function more frequently in elderly patients.
Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis.
Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. ITAGLIP® Plus XR tablet should be temporarily discontinued while patients have restricted food and fluid intake.
Hypoxic States: Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause pre-renal azotemia. When such events occur, discontinue ITAGLIP® Plus XR.
Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism.
Hepatic Impairment: Avoid use in patients with clinical or laboratory evidence of hepatic disease.
Pancreatitis: There have been post marketing reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotizing pancreatitis, patients should be observed carefully, If pancreatitis is suspected, promptly discontinue the treatment.
Heart Failure: Consider the risks and benefits of ITAGLIP® Plus XR prior to initiating treatment in patients at risk for heart failure. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of treatment.
Acute Renal Failure: Before initiation renal function should be assessed, contraindicated in patients with severe renal impairment.
Vitamin B12 Deficiency: Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 measurements at 2 to 3 year intervals and manage any abnormalities accordingly.
Hypoglycaemia with Concomitant Use with Insulin or Insulin Secretagogues: ITAGLIP® Plus XR may increase the risk of hypoglycaemia when combined with insulin and/or an insulin secretagogue (e.g., sulfonylurea). A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycaemia when used in combination.
Hypersensitivity Reactions: If a hypersensitivity reaction is suspected, discontinue and, assess for other potential causes for the event, and institute alternative treatment for diabetes.
Severe and Disabling Arthralgia: There have been post marketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors.
Bullous Pemphigoid: If bullous pemphigoid is suspected, discontinued and referral should be considered for diagnosis and appropriate treatment.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS:
Carbonic Anhydrase Inhibitors: Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic

210mm

120mm

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acidosis. Concomitant use of these drugs like topiramate, zonisamide, acetazolamide or dichlorphenamide may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.
Drugs that Reduce Metformin Clearance: Consider the benefits and risks of concomitant use Ranolazine, vandetanib, dolutegravir, and cimetidine.
Alcohol: Warn patients against alcohol intake while receiving ITAGLIP® Plus XR .
Insulin Secretagogues or Insulin: Coadministration of ITAGLIP® Plus XR with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycaemia.
Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.
Drugs Affecting Glycemic Control: When following drugs are withdrawn observe the patient closely for hypoglycaemia. Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid.

PREGNANCY AND LACTATION:
Pregnancy: The limited available data in pregnant women are not sufficient to inform a drug associated risk for major birth defects and miscarriage.
Lactation: There are no reports of adverse effects on breastfeed infants exposed to metformin. There is no information on the effects of metformin on milk production.
Females and Males of Reproductive Potential: Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

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 has been reported with sitagliptin. In addition, patients should be alerted to the risk of hypoglycaemia when ITAGLIP® Plus XR is used in combination with a sulphonylurea or with insulin.

UNDESIRABLE EFFECTS:
The following adverse reactions are also discussed elsewhere in the labeling. Lactic acidosis, pancreatitis, heart failure, acute renal failure, vitamin B12 deficiency hypoglycaemia with concomitant use with insulin or insulin secretagogues, hypersensitivity reactions, severe and disabling arthralgia, bullous pemphigoid.

Postmarketing Experience: Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to exposure.
- Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome.
- Upper respiratory tract infection, rhabdomyolysis.
- Hepatic enzyme elevations; hepatocellular, and mixed hepatocellular liver injury.
- Acute pancreatitis, including fatal and non-fatal haemorrhagic and necrotizing pancreatitis.
- Worsening renal function, including acute renal failure (sometimes requiring dialysis).
- Severe and disabling arthralgia; bullous pemphigoid; constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus.
- Mouth ulceration; stomatitis; cholestatic.

OVERDOSE:
In the event of an overdose, it is reasonable to employ 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 haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable peritoneal dialysis.

PHARMACOLOGICAL PROPERTIES
PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs.
ATC code: A10BD07
ITAGLIP® Plus XR tablet combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Mechanism of action:
Sitagliptin: Sitagliptin is a DPP-4 inhibitor, which exerts its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. 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.
Metformin: Metformin is a biguanide that improves glycaemic control in patients with type 2 diabetes mellitus, 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.

PHARMACOKINETIC PROPERTIES:
Absorption: After administration of tablets once daily, the median T_{max} value for sitagliptin and metformin at steady state is approximately 3 and 8 hours post dose, respectively. The median T_{max} value for sitagliptin and metformin after administration of a single tablet is 3 and 3.5 hours post dose, respectively.
Distribution:
Sitagliptin: The mean volume of distribution at steady state following a single 100mg intravenous dose of sitagliptin to healthy patients is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).
Metformin: Metformin is negligibly bound to plasma proteins. 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.
Metformin: 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: Approximate 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion.
Metformin: 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.

SHELF LIFE
See expiry on the pack.

AVAILABILITY
ITAGLIP® Plus XR tablet 50/500mg in a pack of 14's
ITAGLIP® Plus XR tablet 50/1000mg in a pack of 14's
ITAGLIP® Plus XR tablet 100/1000mg in a pack of 14's

INSTRUCTIONS
Dosage: As advised by the physician.
To be sold on the prescription of a registered medical practitioner only.
Keep out of the reach of children.
Avoid exposure to heat, light and humidity.
Store between 15 to 30°C.
Improper storage may deteriorate the medicine.

ایٹاگلپ®پلس ایکس آر ٹیبلٹ
(سیٹاگلپٹن فاسفیٹ + میٹ فورمن ہائیڈروکلورائیڈ)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری
سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔

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