Front Page

Incrit™-M

Sitagliptin Phosphate Monohydrate INN
Metformin Hydrochloride BP

50074

Presentation
Incrit-M 500mg Tablet : Each coated tablet contains sitagliptin phosphate monohydrate INN equivalent to 50 mg sitagliptin and metformin hydrochloride BP 500 mg
Incrit-M 1000mg Tablet : Each coated tablet contains sitagliptin phosphate monohydrate INN equivalent to 50 mg sitagliptin and metformin hydrochloride BP 1000 mg

Mechanism of Action
Incrit-M combines two antidiabetic medications with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Sitagliptin
Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.

Metformin hydrochloride
Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances [see Warnings and Precautions]) 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.

Indications and Usage
Incrit-M is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate.

Important Limitations of Use
Incrit-M should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
Incrit-M has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Incrit-M. [See Warnings and Precautions.]

Dosage and Administration
Recommended Dosing
The dosage of Incrit-M should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin. Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.
Incrit-M should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin. Incrit-M must not be split or divided before swallowing.

The following doses are available:

50 mg sitagliptin/500 mg metformin hydrochloride

50 mg sitagliptin/1000 mg metformin hydrochloride.

The recommended starting dose in patients not currently treated with metformin is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin.

The starting dose in patients already treated with metformin should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of metformin already being taken. For patients taking metformin 850 mg twice daily, the recommended starting dose of Incrit-M is 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily.

Patients treated with an insulin secretagogue or insulin

Co-administration of Incrit-M with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia [see Warnings and Precautions].
No studies have been performed specifically examining the safety and efficacy of Incrit-M in patients previously treated with other oral antihyperglycemic agents and switched to Incrit-M. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

Contraindications
Incrit-M (sitagliptin and metformin HCl) is contraindicated in patients with:
Renal impairment (e.g., serum creatinine levels greater than or equal to 1.5 mg/dL for men, greater than or equal to 1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia [see Warnings and Precautions].
Hypersensitivity to metformin hydrochloride.
Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
History of a serious hypersensitivity reaction to Incrit-M or sitagliptin (one of the components of Incrit-M), such as anaphylaxis or angioedema. [See Warnings and Precautions; Adverse Reactions.]

Adverse Reactions
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Most common adverse reaction found in clinical trials were diarrhea, upper respiratory tract infection and headache.

Postmarketing Experience
Additional adverse reactions have been identified during postapproval use of Incrit-M or sitagliptin, one of the components of Incrit-M. These reactions have been reported when Incrit-M or sitagliptin have been used alone and/or in combination with other antihyperglycemic agents. 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 drug exposure.
Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome [see Warnings and Precautions]; upper respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis [see Indications and Usage; Warnings and Precautions]; worsening renal function, including acute renal failure (sometimes requiring dialysis) [see Warnings and Precautions]; constipation; vomiting; headache; arthralgia; myalgia; pain in extremity; back pain.

Warnings 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 Incrit-M; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.
The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily 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. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis.

Back Page

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

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

Assessment of Renal Function
Metformin and sitagliptin are known to be substantially excreted by the kidney.

Metformin hydrochloride
The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, Incrit-M is contraindicated in patients with renal impairment.
Before initiation of Incrit-M and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated (e.g., elderly), renal function should be assessed more frequently and Incrit-M discontinued if evidence of renal impairment is present.

Sitagliptin
There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with Incrit-M and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and Incrit-M discontinued if evidence of renal impairment is present.

Use with Medications Known to Cause Hypoglycemia

Sitagliptin
When sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin [see Adverse Reactions]. Therefore, patients also receiving an insulin secretagogue (e.g., sulfonylurea) or insulin may require a lower dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia [see Dosage and Administration].

Metformin hydrochloride
Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. 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 -adrenergic blocking drugs.

Concomitant Medications Affecting Renal Function or Metformin Disposition
Concomitant medication(s) 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 [see Drug Interactions], should be used with caution.

Hypersensitivity Reactions
There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of Incrit-M. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred 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 Incrit-M, assess for other potential causes for the event, and institute alternative treatment for diabetes. [See Adverse Reactions]
Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Incrit-M.

Use in specific populations
Pregnancy
Pregnancy Category B:
There are no adequate and well-controlled studies in pregnant women with Incrit-M or its individual components; therefore, the safety of Incrit-M in pregnant women is not known. Incrit-M should be used during pregnancy only if clearly needed.

Nursing Mothers
No studies in lactating animals have been conducted with the combined components of Incrit-M. In studies performed with the individual components, both sitagliptin and metformin are secreted in the milk of lactating rats. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Incrit-M is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of Incrit-M in pediatric patients under 18 years have not been established.

Geriatric Use
Because sitagliptin and metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, Incrit-M 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. [See Warnings and Precautions]

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 Incrit-M, as the risk of lactic acidosis may increase.

Cationic Drugs
Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, 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 Incrit-M and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

The Use of Metformin with Other Drugs
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 Incrit-M the patient should be closely observed to maintain adequate glycemic control.

Overdosage
Sitagliptin
During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Maximal mean increases in QTc of 8.0 msec were observed in one study at a dose of 800 mg sitagliptin, a mean effect that is not considered clinically important. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions 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. In clinical studies, approximately 13.5% of the dose was 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
Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see Warnings and Precautions]. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Storage Condition : Keep out of the reach of children. Store below 25°C in a dry place away from light.

Commercial Pack :
Incrit-M 500mg Tablet: 2 x 10's tablet in alu-alu blister pack.
Incrit-M 1000mg Tablet: 3 x 6's tablet in alu-alu blister pack.

Manufactured by:
synovia
Synovia Pharma PLC., Station Road, Tongi, Gazipur.
A Subsidiary of BEXIMCO PHARMACEUTICALS LTD.
531500

Direction Slip artwork legend

Product Name	:	Incrit-M
Code number	:	531500
Dimension	:	L 16.6 x W 6.37 inches
Min. size of text	:	8 pt
Used Colors	:	Black C ■ Pantone 186 C ■