SUMMARY OF PRODUCT CHARACTERISTICS

WARNING: LACTIC ACIDOSIS

Postmarketing 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 non-specific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio, and metformin plasma levels generally >5mcg/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 **ITAGLIP® Plus** and institute general supportive measures in a hospital setting. Prompt haemodialysis is recommended.

1. NAME OF THE PRODUCT

ITAGLIP® Plus (Sitagliptin Phosphate + Metformin HCl) 50/500mg Tablets

ITAGLIP® Plus (Sitagliptin Phosphate + Metformin HCl) 50/850mg Tablets

ITAGLIP® Plus (Sitagliptin Phosphate + Metformin HCl) 50/1000mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ITAGLIP® Plus 50/500mg Tablets
Each film coated tablet contains:
Sitagliptin Phosphate (monohydrate) USP equivalent to Sitagliptin.....50mg
Metformin HCl BP.....500mg

ITAGLIP® Plus 50/850mg Tablets
Each film coated tablet contains:
Sitagliptin phosphate monohydrate USP equivalent to Sitagliptin.....50mg
Metformin HCl BP.....850mg

ITAGLIP® Plus 50/1000mg Tablets
Each film coated tablet contains:
Sitagliptin phosphate monohydrate USP equivalent to Sitagliptin.....50mg
Metformin HCl BP.....1000mg

3. PHARMACEUTICAL FORM

Tablet

Appearance:

ITAGLIP® Plus 50/500mg Tablets: Light green to green color, film coated, capsular shape tablets.

ITAGLIP® Plus 50/850mg Tablets: Light yellow to yellow color, oblong, film coated tablets, plain on both sides.

ITAGLIP® Plus 50/1000mg Tablets: Pink to dark pink color, oblong shape, film coated tablet, plain on both sides.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

For adult patients with type 2 diabetes mellitus: ITAGLIP® 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 those already being treated with the combination of sitagliptin and metformin. **ITAGLIP® 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. **ITAGLIP® 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. **ITAGLIP® Plus** is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

Limitation of use: ITAGLIP® Plus should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

The dose of anti-hyperglycaemic therapy with **ITAGLIP® Plus** should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100mg sitagliptin.

Adults with normal renal function (GFR ≥ 90mL/min):

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 50mg twice daily (100mg 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, **ITAGLIP® 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 50mg twice daily (100mg total daily dose) and a dose of metformin similar to the dose already being taken. When **ITAGLIP® 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 50mg twice daily (100mg 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 50mg twice daily (100mg total daily dose) and a dose of metformin similar to the dose already being taken. When **ITAGLIP® Plus** is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia. For the different doses on metformin, **ITAGLIP® Plus** is available in strengths of 50mg sitagliptin and 850mg metformin hydrochloride or 1000mg metformin hydrochloride. All patients should continue their recommended diet with an adequate distribution of carbohydrate intake during the day.

Special population:

Renal impairment: No dose adjustment is needed for patients with mild renal impairment (glomerular filtration rate [GFR] ≥ 60mL/min). In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3- 6 months. The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR < 60mL/min.

Table: Dose adjustment for renal impaired population

GFR mL/min	Metformin	Sitagliptin
60-89	Maximum daily dose is 3000mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 100mg
45-59	Maximum daily dose is 2000mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 100mg.
30-44	Maximum daily dose is 1000mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 50mg.
<30	Metformin is contraindicated.	Maximum daily dose is 25mg.

Hepatic impairment: Sitagliptin/Metformin hydrochloride must not be used in patients with hepatic impairment.

Elderly: As metformin and sitagliptin are excreted by the kidney, Sitagliptin/Metformin hydrochloride should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly.

Paediatric population: Sitagliptin/Metformin hydrochloride should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. Sitagliptin/Metformin hydrochloride has not been studied in paediatric patients under 10 years of age.

Method of administration:

Oral use. **ITAGLIP® Plus** should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

4.3. CONTRAINDICATIONS:

Sitagliptin/Metformin hydrochloride is contraindicated in patients with:

- Hypersensitivity to the active substances or to any of the excipients;
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis);
- Diabetic pre-coma.
- Severe renal failure (GFR< 30mL/min);
- Acute conditions with the potential to alter renal function such as:
  - Dehydration,
  - Severe infection,
  - Shock,
  - Intravascular administration of iodinated contrast agents;
- 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.
- Breast-feeding.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

General: Sitagliptin/Metformin hydrochloride should not be used in patients with type 1 diabetes and must not be used for the treatment of diabetic ketoacidosis.

Acute pancreatitis: Patients be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain, very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, Sitagliptin/Metformin hydrochloride and other potentially suspect medicinal products should be discontinued. Caution should be exercised in patients with a history of pancreatitis.

Lactic acidosis: Lactic acidosis, a rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. In case of dehydration (severe vomiting, diarrhea, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional isrecommended. Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis. Lactic acidosis is characterized by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (> 5mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function: GFR should be assessed before treatment initiation and regularly thereafter. Sitagliptin/metformin hydrochloride is contraindicated in patients with GFR <30mL/min and should be temporarily discontinued during conditions with the potential to alter renal function.

Hypoglycaemia: Patients receiving sitagliptin/metformin hydrochloride in combination with a sulphonylurea or with insulin may be at risk for hypoglycaemia.

Hypersensitivity reactions: Post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin have been reported. 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, sitagliptin/metformin hydrochloride should be discontinued.

Bullous pemphigoid: There have been post-marketing reports of bullous pemphigoid in patients taking DPP-4 inhibitors including sitagliptin. If bullous pemphigoid is suspected, sitagliptin/metformin hydrochloride should be discontinued.

Surgery: Sitagliptin/Metformin hydrochloride must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Administration of iodinated contrast agent: Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Sitagliptin/metformin hydrochloride should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours.

Change in clinical status of patients with previously controlled type 2 diabetes: A patient with type 2 diabetes previously well controlled on sitagliptin/metformin hydrochloride 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, treatment must be stopped immediately.

Vitamin B12 Deficiency: Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS:

Co-administration of multiple doses of sitagliptin (50mg twice daily) and metformin (1000mg twice daily) did not meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes.

Carbonic Anhydrase Inhibitors: Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Sitagliptin/Metformin hydrochloride may increase the risk of lactic acidosis.

Concomitant use not recommended: ***Alcohol:*** Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Combinations requiring precautions for use: Some medicinal products can adversely affect renal function, which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary. Concomitant use of medicinal products that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use. Close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when such products are co-administered. Glucocorticoids (given by systemic and local routes) beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation. ACE-inhibitors may decrease the blood glucose levels. If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Effects of other medicinal products on sitagliptin:

In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin. Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD). For this reason, it is possible that 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 in a clinical study.

Digoxin: Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or Sitagliptin/metformin hydrochloride is recommended. Limited data suggest that the use of in pregnant women is not associated with an increased risk of birth defects. Animal studies with have not produced any evidence of harmful effects on pregnancy, embryonic or foetal development, parturition or postnatal development. Sitagliptin and combination tablets should not be used during pregnancy. If patients plan to become pregnant or find out that she is pregnant, treatment should be stopped and the patient treated with insulin as soon as possible.

Ciclosporin: Co-administration of a single 100mg oral dose of sitagliptin and a single 600mg oral dose of ciclosporin increased the AUC and C_{max} of sitagliptin by approximately 29 % and 68 %, respectively. These changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: Animal data do not suggest an effect of treatment with sitagliptin on male and female fertility. Human data are lacking.

Pregnancy: Sitagliptin/Metformin hydrochloride should not be used during pregnancy. If a patient hopes to become pregnant or if a pregnancy occurs, treatment should be discontinued and the patient switched to insulin treatment as soon as possible.

Breast-feeding: It is not known whether sitagliptin is excreted in human milk. Sitagliptin/Metformin hydrochloride must therefore not be used in women who are breast-feeding.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Sitagliptin/Metformin hydrochloride 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 hydrochloride is used in combination with a sulphonylurea or with insulin.

4.8. UNDESIRABLE EFFECTS:

Sitagliptin and Metformin:

Adverse reactions are listed below as MedDRA preferred term by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000) and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders: ***Rare:*** Thrombocytopenia.

Immune system: ***Frequency not known:*** Hypersensitivity reactions including anaphylactic responses.

Metabolism and nutrition disorders: ***Common:*** Hypoglycemia, Vitamin B12 decreases/deficiency.

Nervous system disorders: ***Uncommon:*** Somnolence. ***Frequency not known:*** Headache.

Respiratory, thoracic and mediastinal disorders: ***Frequency not known:*** Interstitial lung disease.

Gastrointestinal disorders: ***Common:*** Nausea, flatulence, vomiting. ***Uncommon:*** Diarrhoea, constipation, upper abdominal pain. ***Frequency not known:*** Acute pancreatitis, fatal and non-fatal haemorrhagic and necrotizing pancreatitis.

Skin and subcutaneous tissue disorders: ***Uncommon:*** Pruritus. ***Frequency not known:*** Angioedema, rash, urticaria, cutaneous vasculitis, exfoliative skin conditions including Stevens-Johnson syndrome, bullous pemphigoid.

Musculoskeletal and connective tissue disorders: ***Frequency not known:*** Arthralgia, myalgia, back pain, arthropathy, pain in extremity

Renal and Urinary disorders: ***Frequency not known:*** Impaired renal function, acute renal failure.

Hepatobiliary disorders: ***Frequency not known:*** Hepatic enzyme elevations, cholestatic, hepatocellular, and hepatocellular liver injury.

4.9. OVERDOSE:

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 haemodialysis. In clinical studies, approximately 13.5% of the dose was 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 gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Medicinal products used in diabetes, Combinations of oral blood glucose lowering medicinal products, **ATC code:** A10BD07.

ITAGLIP® Plus combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: sitagliptin fumarate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Sitagliptin:

Mechanism of action: Sitagliptin fumarate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). 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. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. When blood glucose levels are low, insulin release is not enhanced and glucagon secretion is not suppressed. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulphonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, alpha-glucosidase inhibitors, and amylin analogues. In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

Metformin:

Mechanism of action: Metformin is a biguanide with anti-hyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:

- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

5.2. PHARMACOKINETICS:

Sitagliptin/Metformin hydrochloride: A bioequivalence study in healthy subjects demonstrated that sitagliptin/metformin hydrochloride combination tablets are bioequivalent to co-administration of sitagliptin and metformin hydrochloride as individual tablets. The following statements reflect the pharmacokinetic properties of the individual active substances of ITAGLIP® Plus.

Sitagliptin:

Absorption: Following oral administration of a 100mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52μM•hr, C_{max} was 950nM. 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.

Distribution: The mean volume of distribution at steady state following a single 100mg intravenous dose of sitagliptin to healthy subjects 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. In vitro data showed that sitagliptin is not an inhibitor of CYP isoenzymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Elimination: 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. The apparent terminal t½ following a 100mg oral dose of sitagliptin was approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The renal clearance was approximately 350mL/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. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. In vitro, sitagliptin did not inhibit OAT3 (IC50=160μM) or p-glycoprotein (up to 250μM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

Metformin:

Absorption: After an oral dose of metformin, Tmax is reached in 2.5h. Absolute bioavailability of a 500mg 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 24-48h and are generally less than 1μg/mL. In controlled clinical studies, maximum metformin plasma levels (C_{max}) did not exceed 5μg/mL, even at maximum doses. Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850mg, a 40% lower plasma peak concentration, a 25% decrease in AUC and a 35min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Distribution: 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 ranged between 63 – 276L.

Metabolism: Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination: Renal clearance of metformin is > 400mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3. PRECLINICAL SAFETY DATA:

No animal studies have been conducted with sitagliptin/metformin hydrochloride. In 16-week studies in which dogs were treated with either metformin alone or a combination of metformin and sitagliptin, no additional toxicity was observed from the combination. The NOEL in these studies was observed at exposures to sitagliptin of approximately 6 times the human exposure and to metformin of approximately 2.5 times the human exposure.

The following data are findings in studies performed with sitagliptin or metformin individually.

Sitagliptin: Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no effect level for this finding was 58-fold based on the 14-week rat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.

Metformin: Preclinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

ITAGLIP® Plus 50/500mg Tablets:

Core:

- Microcrystalline cellulose
- Crospovidone
- Poly vinyl pyrrolidone
- Sodium lauryl sulphate
- Apple green lake color
- Sodium stearyl fumarate
- Silicon dioxide fumed
- Magnesium stearate
- Purified water

Coating:

- Hydroxypropyl methyl cellulose
- Isopropyl alcohol
- Titanium dioxide
- Talcum powder
- Poly vinyl pyrrolidone
- Polyethylene glycol
- Purified water
- Apple green lake color

ITAGLIP® Plus 50/850mg Tablets:

Core:

- Microcrystalline cellulose
- Crospovidone
- Poly vinyl pyrrolidone
- Sodium lauryl sulphate
- Sodium stearyl fumarate
- Yellow iron oxide color
- Purified water

Coating:

- Sheffcoat
- Simethicone
- Yellow iron oxide color
- Purified water

ITAGLIP® Plus 50/1000mg Tablets:

Core:

- Crospovidone
- Poly vinyl pyrrolidone
- Sodium lauryl sulphate
- Sodium stearyl fumarate
- Allura red lake color
- Silicon dioxide
- Magnesium stearate
- Purified water

Coating:

- Sheffcoat
- Allura red lake color
- Purified water

SUMMARY OF PRODUCT CHARACTERISTICS

6.2. INCOMPATIBILITIES:
Not applicable.

6.3. SHELF LIFE:
See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Avoid exposure to heat, light and humidity. Store between 15 to 30°C. Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:
ITAGLIP® Plus 50/500mg Tablets: Alu/Alu blister, pack size is 14's.
ITAGLIP® Plus 50/850mg Tablets: Alu/Alu blister, pack size is 14's.
ITAGLIP® Plus 50/1000mg Tablets: Alu/Alu blister, pack size is 14's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:
ITAGLIP® Plus 50/500mg Tablets: BP Specs.
ITAGLIP® Plus 50/850mg Tablets: BP Specs.
ITAGLIP® Plus 50/1000mg Tablets: BP Specs.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

8. MARKETING AUTHORISATION NUMBER(S)
ITAGLIP® Plus 50/500mg Tablets: 075855
ITAGLIP® Plus 50/850mg Tablets: 094916
ITAGLIP® Plus 50/1000mg Tablets: 088250

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
ITAGLIP® Plus 50/500mg Tablets: 10th April, 2013
ITAGLIP® Plus 50/850mg Tablets: 20th February, 2019
ITAGLIP® Plus 50/1000mg Tablets: 16th April, 2018

10. DATE OF REVISION OF THE TEXT

ایٹاگلپ®+پلس ٹیبلٹ

(سیٹاگلپٹن فاسفیٹ + میٹ فورمن ھائیڈروکلورائیڈ)

ہدایات:

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