ITAGLIP® Tablet

(Sitagliptin Phosphate)

QUALITATIVE AND QUANTITATIVE COMPOSITION

ITAGLIP® 50mg Tablets
Each film coated tablet contains:
Sitagliptin Phosphate USP
equivalent to Sitagliptin.....50mg

ITAGLIP® 100mg Tablet
Each film coated tablet contains:
Sitagliptin Phosphate USP
equivalent to Sitagliptin.....100mg

PHARMACEUTICAL FORM

Tablet

Appearance:

ITAGLIP® 50mg Tablets: Light purple to dark purple colored, round biconvex film coated tablets.

ITAGLIP® 100mg Tablet: Orange to dark orange colored, round biconvex film coated tablets.

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS:

For adult patients with type 2 diabetes mellitus, **ITAGLIP®** is indicated to improve glycaemic control:

As monotherapy:

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

As dual oral therapy in combination with:

- Metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- A sulphonylureas when diet and exercise plus maximal tolerated dose of a sulphonylureas alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- A peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e. a thiazolidinedione) when the use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.

As triple oral therapy in combination with:

- Sulphonylureas and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.
- A PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

ITAGLIP® is also indicated as an add-on to insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.

POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

The dose is 100mg 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 **ITAGLIP®** administered concomitantly. When **ITAGLIP®** is used in combination with sulphonylureas or with insulin, a lower dose of the sulphonylureas or insulin may be considered to reduce the risk of hypoglycemia. If a dose of **ITAGLIP®** is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

Special populations:

Renal impairment: When considering the use of sitagliptin in combination with another anti-diabetic medicinal product, its conditions for use in patients with renal impairment should be checked. For patients with mild renal impairment (glomerular filtration rate [GFR] ≥ 60 to < 90mL/min), no dose adjustment is required. For patients with moderate renal impairment (GFR ≥ 45 to < 60mL/min), no dosage adjustment is required. For patients with moderate renal impairment (GFR ≥ 30 to < 45mL/min), the dose of is 50mg once daily. For patients with severe renal impairment (GFR ≥ 15 to <30mL/min) or with end-stage renal disease (ESRD) (GFR < 15mL/min), including those requiring haemodialysis or peritoneal dialysis, the dose of **ITAGLIP®** is 25mg once daily. Treatment may be administered without regard to the timing of dialysis. Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of **ITAGLIP®** and periodically thereafter.

Hepatic impairment: No dose adjustment is necessary for patients with mild to moderate hepatic impairment. **ITAGLIP®** has not been studied in patients with severe hepatic impairment and care should be exercised. However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

Elderly: No dose adjustment is necessary based on age.

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

Method of administration:

ITAGLIP® can be taken with or without food.

CONTRAINDICATIONS:

Hypersensitivity to the active substance or any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

General: Sitagliptin phosphate should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Acute pancreatitis: The use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin (with or without supportive treatment), but very rare cases of necrotizing or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, sitagliptin phosphate and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, sitagliptin phosphate should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Hypoglycaemia when used in combination with other anti-hyperglycemic medicinal products: In clinical trials of sitagliptin phosphate as monotherapy and as part of combination therapy with medicinal products not known to cause hypoglycemia (i.e. metformin and/or a PPARγ agonist), rates of hypoglycemia reported with sitagliptin were similar to rates in patients taking placebo. Hypoglycaemia has been observed when sitagliptin was used in combination with insulin or sulphonylureas. Therefore, to reduce the risk of hypoglycemia, a lower dose of sulphonylureas or insulin may be considered.

Renal impairment: Sitagliptin is renally excreted. To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with GFR < 45mL/min, as well as in ESRD patients requiring haemodialysis or peritoneal dialysis. When considering the use of sitagliptin in combination with another anti-diabetic medicinal product, its conditions for use in patients with renal impairment should be checked.

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 some reports occurring after the first dose. If a hypersensitivity reaction is 5 suspected, sitagliptin phosphate should be discontinued. Other potential causes for the event should be assessed, and alternative treatment for diabetes initiated.

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 phosphate should be discontinued.

Sodium: This medicinal product contains less than 1mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

Effects of other medicinal products on sitagliptin:

Metformin: Co-administration of multiple twice-daily doses of 1,000mg metformin with 50mg sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

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.

Effects of sitagliptin on other medicinal products:

Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0.25mg digoxin concomitantly with 100mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased on average by 11%, and the plasma C_{max} on average by 18%. 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.

In vitro: Data suggest that sitagliptin does not inhibit nor induce CYP450 isoenzymes. In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing in vivo evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Sitagliptin may be a mild inhibitor of p-glycoprotein in vivo.

FERTILITY, PREGNANCY AND LACTATION:

Fertility: Not known.

Pregnancy: There is no adequate data on the use of sitagliptin in pregnant women. Due to a lack of human data, sitagliptin phosphate should not be used during pregnancy.
Breast-feeding: It is unknown whether sitagliptin is excreted in human breast milk. Sitagliptin phosphate should not be used during breast-feeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Sitagliptin phosphate 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. In addition, patients should be alerted to the risk of hypoglycemia when sitagliptin phosphate is used in combination with sulphonylureas or with insulin.

UNDESIRABLE EFFECTS:
Adverse reactions are listed below (Table 1) by system organ class and 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 disorders: ***Frequency not known:*** Hypersensitivity reactions including anaphylactic responses.
Metabolism and nutrition disorders: ***Common:*** Hypoglycemia.
Nervous system disorders: ***Common:*** Headache. ***Uncommon:*** Dizziness.
Respiratory, thoracic, and mediastinal disorders: ***Frequency not known:*** Interstitial lung disease.
Gastrointestinal disorders: ***Uncommon:*** Constipation. ***Frequency not known:*** Vomiting, 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.
Renal and Urinary disorders: ***Frequency not known:*** Impaired renal function, acute renal failure

OVERDOSE:
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. Sitagliptin is modestly dialysable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

PHARMACOLOGICAL PROPERTIES
PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Drugs used in diabetes, Dipeptidyl peptidase 4 (DPP-4) inhibitors, **ATC code:** A10BH01.
Mechanism of action: Sitagliptin phosphate is a member of a class of oral anti-hyperglycemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors. The improvement in glycaemic control observed with this medicinal product may be mediated by enhancing the levels of active incretin 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. 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.

PHARMACOKINETICS:
Absorption: Following oral administration, 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 phosphate may be administered with or without food.
Distribution: The mean volume of distribution at a 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%).
Biotransformation: Sitagliptin is primarily eliminated unchanged in the 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 isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19, or 2B6, and is not an inducer of CYP3A4 and CYP1A2.
Elimination: 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.

PRECLINICAL SAFETY DATA:
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. Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with the induction of hepatic neoplasia in rats, this increased incidence of hepatic tumors in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans. No adverse effects upon fertility were observed in male and female rats given sitagliptin prior to and throughout mating. In a pre-/postnatal development study performed in rats sitagliptin showed no adverse effects. Reproductive toxicity studies showed a slight treatment-related increased incidence of fetal rib malformations (absent, hypoplastic, and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

PHARMACEUTICAL PARTICULARS
LIST OF EXCIPIENTS:
ITAGLIP® 50mg Tablets:
● Microcrystalline cellulose ● Dicalcium phosphate dihydrate ● Crosscarmellose sodium ● Polyvinyl pyrrolidone ● Silicon dioxide fumed ● Sodium stearyl fumarate ● Magnesium Stearate ● Hypromellose E5 ● Titanium dioxide ● Talcum ● Polyethylene glycol ● Amaranth lake color
ITAGLIP® 100mg Tablet:
● Microcrystalline cellulose ● Dicalcium phosphate dihydrate ● Crosscarmellose sodium ● Polyvinyl pyrrolidone ● Silicon dioxide fumed ● Sodium stearyl fumarate ● Magnesium Stearate ● Hypromellose E5 ● Titanium dioxide ● Talcum ● Polyethylene glycol ● Sunset yellow lake color

INCOMPATIBILITIES:
Not applicable

SHELF LIFE:
See expiry on the pack.

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 chlildren.

NATURE AND CONTENTS OF CONTAINER:
ITAGLIP® 50mg Tablets: Alu/Alu blister, pack size 14's.
ITAGLIP® 100mg Tablet: Alu/Alu blister, pack size 14's.

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

DRUG PRODUCT SPECIFICATIONS:
USP Specs.

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

MARKETING AUTHORISATION NUMBER(S)
ITAGLIP® 50mg Tablets: 075854
ITAGLIP® 100mg Tablet: 075853

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
ITAGLIP® 50mg Tablets: 10th April, 2013
ITAGLIP® 100mg Tablet: 10th April, 2013

DATE OF REVISION OF THE TEXT

ایٹاگلپ® ٹیبلٹ

(سیٹا گلپٹن فاسفیٹ)

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 دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں

ورنہ دوا خراب ہو جائیگی۔