SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICAL PRODUCT

1.1 **PRODUCT NAME**: GLIPITA-M 50/500

(Sitagliptin 50 mg and Metformin Hydrochloride 500 mg Caplets)

GLIPITA-M 50/1000

(Sitagliptin 50 mg and Metformin Hydrochloride 1000 mg Caplets)

1.2 **STRENGTH**

GLIPITA-M 50/500 (Sitagliptin 50 mg and Metformin Hydrochloride 500 mg Caplets)

Each film coated caplet contains:

Sitagliptin Phosphate Monohydrate USP Equivalent to Sitagliptin. 50 mg

Metformin Hydrochloride USP 500 mg

Colour: **Sunset Yellow, Aluminium Lake, FD & C Red, Allura Red** & Titanium Dioxide Excipients. q.s.

GLIPITA-M 50/1000 (Sitagliptin 50 mg and Metformin Hydrochloride 1000 mg Caplets)

Each film coated caplet contains:

Sitagliptin Phosphate Monohydrate USP Equivalent to Sitagliptin. 50mg

Metformin Hydrochloride USP 1000 mg

Colour: FD & C Yellow, Sunset Yellow, Iron Oxide Yellow, Allura Red & Titanium Dioxide Excipients. q.s.

1.3 **PHARMACEUTICAL DOSAGE FORM**

Film Coated caplets

2. QUALITATIVE & QUANTITATIVE COMPOSITION:

GLIPITA -M 50/500 (Sitagliptin 50 mg and Metformin Hydrochloride 500 mg caplets)

Each film coated caplet contains:

Sitagliptin Phosphate Monohydrate USP Equivalent to Sitagliptin. 50 mg

Metformin Hydrochloride USP 500 mg

Colour: **Sunset Yellow, Aluminium Lake, FD & C Red, Allura Red** & Titanium Dioxide-Excipients. q.s.

GLIPITA-M 50/1000 (Sitagliptin 50 mg and Metformin Hydrochloride 1000 mg caplets)

Each film coated caplet contains:

Sitagliptin Phosphate Monohydrate USP Equivalent to Sitagliptin. 50 mg

Metformin Hydrochloride USP 1000 mg

Colour: FD & C Yellow, Sunset Yellow, Iron Oxide Yellow, Allura Red & Titanium Dioxide Excipients. q.s.

For a full list of excipients, see section 6.1 of SmPC

3. **PHARMACEUTICAL FORM:**

GLIPITA-M 50/500 (Sitagliptin 50 mg and Metformin Hydrochloride 500 mg caplets)

Orange colored, oblong shaped film coated caplets, engraved **"BPL"** on one side and plain on the other side, free from any visual defects.

GLIPITA-M 50/1000 (Sitagliptin 50 mg and Metformin Hydrochloride 1000 mg caplets)

An orange color, oblong shaped film coated tablet, engraved "**BPL"** on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

GLIPITA-M is indicated as an adjunct to diet and exercise to improve glycemic control

in adults with type 2 diabetes mellitus.

Limitations of Use

GLIPITA-M should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

GLIPITA-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 GLIPITA-M.

4.2. **POSOLOGY AND METHOD OF ADMINISTRATION**:

Recommended Dosing

The dosage of GLIPITA-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 hydrochloride (Metformin HCl). Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.

GLIPITA-M should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to Metformin. GLIPITA-M must not be split or divided before swallowing.

The starting dose of GLIPITA-M should be based on the patient's current regimen.

GLIPITA-M should be given twice daily with meals. The following doses are available:

50 mg sitagliptin/500 mg Metformin HCl

50 mg sitagliptin/1000 mg Metformin HCl.

The recommended starting dose in patients not currently treated with Metformin is 50mg sitagliptin/500 mg Metformin HCl 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 GLIPITA-M is 50 mg sitagliptin/1000 mg Metformin HCl twice daily. No studies have been performed specifically examining the safety and efficacy of GLIPITA-M in patients previously treated with other oral antihyperglycemic agents and switched to GLIPITA-M. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

Pediatric Use

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

Geriatric Use

GLIPITA-M

Because sitagliptin and are substantially excreted by the kidney, and because aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients.

Recommendations for Use in Renal Impairment

Assess renal function prior to initiation of GLIPITA-M and periodically thereafter.

GLIPITA-M is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m2.

GLIPITA-M is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m2 because these patients require a lower dosage of sitagliptin than what is available in the fixed combination GLIPITA-M product.

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue GLIPITA-M at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m2; 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 GLIPITA-M if renal function is stable.

4.3 **CONTRAINDICATIONS:**

GLIPITA-M is contraindicated in patients with:

• Severe renal impairment (eGFR below 30 mL/min/1.73 m2)

• Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.

• History of a serious hypersensitivity reaction to Sitagliptin / Combination, sitagliptin, or such as anaphylaxis or angioedema.

Radiological Studies with Contrast

Administration of intravascular iodinated contrast agents in -treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop GLIPITA-M at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra- arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart GLIPITA-M if renal function is stable.

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. GLIPITA-M should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States

Several of the post marketing cases of -associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and

hypoxemia).

Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue Sitagliptin / Combination.

Excessive Alcohol Intake

Alcohol potentiates the effect of on lactate metabolism and this may increase the risk of -associated lactic acidosis. Warn patients against excessive alcohol intake while receiving GLIPITA-M.

Hepatic Impairment

Patients with hepatic impairment have developed with cases of -associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of GLIPITA-M n 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 hemorrhagic or necrotizing pancreatitis, in patients taking GLIPITA-M. After initiation of GLIPITA-M, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, GLIPITA-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 GLIPITA-M.

Heart Failure

An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of

the DPP-4 inhibitor class.

These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of GLIPITA-M prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of GLIPITA-M.

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

HCl

GLIPITA-M is contraindicated in patients with severe renal impairment.

Sitagliptin

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

Vitamin B12 Deficiency

In controlled clinical trials of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia but appears to be rapidly

reversible with discontinuation of or vitamin B12 supplementation. 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 in patients on GLIPITA-M and manage any abnormalities.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes

A patient with type 2 diabetes previously well controlled on GLIPITA-M 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 levels. If acidosis of either form occurs, GLIPITA-M must be stopped immediately and other appropriate corrective measures initiated.

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. 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 hypoglycaemia.

Metformin HCl

Hypoglycemia does not occur in patients receiving 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 β- adrenergic blocking drugs.

Loss of Control of Blood Glucose

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold GLIPITA-M and temporarily administer insulin. GLIPITA-M may be reinstituted after the acute episode is resolved.

Hypersensitivity Reactions

There have been post marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of GLIPITA-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 GLIPITA-M, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Angioedema has also been reported with other 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 GLIPITA-M.

Severe and Disabling Arthralgia

There have been post marketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years.

Patients experienced relief of symptoms upon discontinuation of the medication. A

subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor.

Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid

Post marketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving GLIPITA-M. If bullous pemphigoid is suspected, GLIPITA-M should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with GLIPITA-M.

4.5 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

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 GLIPITA-M may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.

Drugs that Reduce Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of (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 and may increase the risk for lactic acidosis.

Consider the benefits and risks of concomitant use.

Alcohol

Alcohol is known to potentiate the effect of on lactate metabolism. Warn patients against excessive alcohol intake while receiving GLIPITA-M.

Insulin Secretagogues or Insulin

Co administration of GLIPITA-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.

Use of 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 GLIPITA-M the patient should be closely observed to maintain adequate glycemic control.

Digoxin

There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (Cmax, 18%) of digoxin with the co administration of 100 mg sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or GLIPITA-M 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 fetal 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.

4.6. **PREGNANCY AND LACTATION**

BREST FEEDING

No studies have been carried out in lactating animals with the combination of the active Substances of this medicine. Studies with each of the active substances have shown that sitagliptin and are excreted in the milk in lactating rats is excreted in small amounts in human breast milk. It is not known whether sitagliptin is excreted in human breast milk. Sitagliptin and combination tablets should therefore not be used during breast-feeding.

FERTILITY

Animal data have not shown any effect of sitagliptin on male and female fertility. There are no data in humans.

4.7. **EFFECTS ON ABILITY TO DRIVE AND USE MACHINE:**

Sitagliptin and Combination tablet has no or negligible influence on the ability to drive and use machines. However, when driving and using machines, it should be taken into account that dizziness and drowsiness have been reported with Sitagliptin.

Additionally, patients should be cautioned about the risk of hypoglycaemia when

GLIPITA-M is given in combination with a sulfonylurea or insulin.

4.8. **UNDESIRABLE EFFECTS:**

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.

Sitagliptin and Immediate-Release Co-administration in Patients with Type 2 Diabetes Inadequately Controlled On Diet and Exercise

Table 1 summarizes the most common (≥5% of patients) adverse reactions reported (regardless of investigator assessment of causality) in a 24-week placebo-controlled factorial study in which sitagliptin and immediate-release were co-administered to patients with type 2 diabetes inadequately controlled on diet and exercise.

Table 1: Sitagliptin and Immediate-Release Co-administered to Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo) *

Sitagliptin Add-on Therapy In Patients With Type 2 Diabetes Inadequately Controlled On Immediate-Release Alone

In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice daily immediate-release regimen, there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo. Discontinuation of therapy due to clinical adverse reactions was similar to the placebo treatment group (sitagliptin and immediate-release, 1.9%; placebo and immediate-release, 2.5%).

Gastrointestinal Adverse Reactions

The incidences of pre-selected gastrointestinal adverse experiences in patients treated with sitagliptin and immediate-release were similar to those reported for patients treated with immediate-release alone.

Pre-selected Gastrointestinal Adverse Reactions (Regardless of Investigator Assessment of Causality) Reported in Patients with Type 2 Diabetes Receiving Sitagliptin and Immediate-Release

Hypoglycemia

In all (N=5) studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required although most (77%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤70 mg/dL. When the combination of sitagliptin and immediate-release was co- administered with a sulfonylurea or with insulin, the percentage of patients reporting at least one adverse reaction of hypoglycemia was higher than that observed with placebo and immediate-release co-administered with a sulfonylurea or with insulin.

Vital Signs and Electrocardiograms

With the combination of sitagliptin and immediate-release, no clinically meaningful changes in vital signs or in electrocardiogram parameters (including the QTc interval) were observed.

Pancreatitis

In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of acute pancreatitis was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for

sitagliptin and 4 patients with an event in 3942 patient-years for control).

Sitagliptin

The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo was nasopharyngitis.

Metformin HCl

The most common (>5%) established adverse reactions due to initiation of therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

Laboratory Tests Sitagliptin

The incidence of laboratory adverse reactions was similar in patients treated with sitagliptin and (7.6%) compared to patients treated with placebo and (8.7%). In most but not all studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs placebo; mean baseline WBC approximately 6600 cells/microL) was observed due to a small increase in neutrophils. This change in laboratory parameters is not considered to be clinically relevant.

Metformin HCl

In controlled clinical trials of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately.

7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of or vitamin B12 supplementation.

Post - marketing Experience

Additional adverse reactions have been identified during post approval use of sitagliptin

with, sitagliptin, or 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; upper respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and nonfatal hemorrhagic 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; cholestatic, hepatocellular, and mixed hepatocellular liver injury.

4.9. **OVERDOSAGE**

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. 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.

Overdose of Metformin HCl has occurred, including ingestion of amounts greater than 50 grams.

Hypoglycemia was reported in approximately 10% of cases, but no causal association with Metformin HCl has been established. Lactic acidosis has been reported in

approximately 32% of overdose cases 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 Overdosage is suspected.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacodynamics:

Mechanism of Action GLIPITA-M

GLIPITA-M combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus: sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and Metformin HCl, 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 HCl

Is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

PHARMACODYNAMIC

Sitagliptin

In published studies conducted in patients with type 2 diabetes mellitus, administration of sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia.

Sitagliptin and Metformin HCl Co administration

As per innovator data consisting of two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas alone increased active and total GLP-1 concentrations to similar extents.

Coadministration of sitagliptin and had an additive effect on active GLP-1 concentrations.

Sitagliptin, but not, increased active GIP concentrations. It is unclear what these findings mean for changes in glycemic control in patients with type 2 diabetes mellitus.

5.2. **PHARMACOKINETICS PROPERTIES:**

Pharmacokinetics:

Sitagliptin

The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes mellitus. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 Mhr, Cmax was 950 nM, and apparent terminal half-life (t1/2) was 12.4 hours. Plasma AUC of sitagliptin increased in a dose-proportional manner and increased approximately 14% following 100 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes mellitus.

Absorption

Sitagliptin

After oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed with peak plasma concentrations (median Tmax) occurring 1 to 4 hours post

dose. The absolute bioavailability of sitagliptin is approximately 87%.

Effect of Food

Co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin.

Metformin HCl

The absolute bioavailability of Metformin HCl 500-mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of Metformin HCl tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg (approximately 1.3 times the maximum recommended daily dosage), indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Effect of Food

Food decreases the extent of and slightly delays the absorption of, as shown by approximately a 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850-mg tablet of with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Sitagliptin

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

Metformin HCl

The apparent volume of distribution (V/F) of following single oral doses of Metformin HCl tablets 850 mg averaged 654 ± 358 L. is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of Metformin HCl tablets, steady-state plasma concentrations of are reached within 24-48 hours and are generally <1 mcg/mL.

Elimination

Sitagliptin

Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. The apparent terminal t1/2 following a 100 mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

Metformin HCl

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.

Metabolism

Sitagliptin

Following a [14C] 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.

Metformin HCl

Intravenous single-dose studies in normal subjects demonstrate that is excreted unchanged in the urine and does not undergo hepatic metabolism.

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with was found in either male or female mice. Similarly, there was no tumorigenic potential observed with in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of in the following in vitro tests: Ames test (S. typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative. Fertility of male or female rats was unaffected by when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

GLIPITA-M 50/500 (Sitagliptin 50 mg and Metformin Hydrochloride 500 mg Caplets), Microcrystalline Cellulose 69.37mg, Sodium Lauryl Sulphate 13.70mg, Povidone K 30 30.83mg, Sodium Stearyl Fumarate 6.85mg,Isopropyl Alcohol 120mg, Opadry Ii,Polyvinyl Alcohol, Talc, Titanium Dioxide, Macrogol, Sunset Yellow, Aluminium Lake, Fd & C Red, Allura Red, Carnauba Wax

GLIPITA-M 50/1000 (Sitagliptin 50 mg and Metformin Hydrochloride 1000 mg Caplets), Microcrystalline Cellulose, Sodium Lauryl Sulphate, Povidone, Sodium Stearyl Fumarate,

Isopropyl Alcohol, Titanium Dioxide, Magnesium Stearate, Opadry Ii (Orange), Lecithin, FD & C Yellow, Sunset Yellow, Iron Oxideyellow, Allura Red, Carnauba Wax, Purified Water

6.2. **INCOMPATIBILITIES**

Not applicable

6.3. **SHELF LIFE**

24 months

6.4 **SPECIAL PRECAUTIONS FOR STORAGE**

Store below 30°C.

6.5. **NATURE AND CONTENTS OF CONTAINER**

10 caplets in Alu-Alu blister pack, 3 such blister in a printed carton along with Pack Insert.

6.6. **SPECIAL PRECAUTIONS FOR DISPOSAL**

Not applicable

7. **MARKETING AUTHORIZATION HOLDER:**

Beximco Pharmaceuticals Ltd

126, Kathaldia, Auchpara, Tongi, Gazipur,

Bangladesh