Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Silinor-M 50/1000 (Sitagliptin 50 mg & Metformin Hydrochloride 1000mg) film coated tablet

2. Qualitative and quantitative composition

Each film coated tablet contains **;**Sitagliptin 50 mg as Sitagliptin Phosphate Monohydrate INN 64.25 mg and Metformin Hydrochloride BP 1000 mg.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

brown colored, oblong shaped film coated tablet one side break line and other side plain which is packed in a Blister.

4. Clinical Particulars

4.1 Therapeutic Indications

It 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.

4.2 Posology and method of Administration

Dose of this combination 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.

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

Sitagliptin/Metformin combination should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to Metformin. 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 this combination is 50 mg Sitagliptin/1000 mg Metformin hydrochloride twice daily.

Special populations

Renal impairment

No dose adjustment is needed for patients with mild renal impairment (glomerular filtration rate [GFR] ≥ 60 mL/min). A GFR

should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. 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 (see section 4.4) should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.
If no adequate strength of Janumet is available, individual monocomponents should be used instead of the fixed-dose combination.

Hepatic impairment
Janumet must not be used in patients with hepatic impairment

Elderly
As metformin and sitagliptin are excreted by the kidney, Janumet 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
Janumet should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. Currently available data are described in sections 4.8, 5.1, and 5.2. Janumet has not been studied in paediatric patients under 10 years of age.

Method of administration

Janumet should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

4.3 Contraindication

Combination (Sitagliptin/Metformin) is contraindicated in patients with: hepatic impairment, breast feeding, renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels 1.5 mg/dL [males), 1.4 mg/dL [females]. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. History of serious hypersensitivity reaction to the combination or sitagliptin, such as anaphylaxis or angioedema.

4.4. Special warnings and precautions for use

Do not use the combination of Sitagliptin & Metformin in patients with *hepatic disease*. Before initiating the combination and at least

annually thereafter, assess renal function and verify as normal. May need to discontinue the combination and temporarily use insulin during periods of stress and decreased intake of fluids and food as may occur with fever, trauma, infection or surgery.

Hypoglycaemia
Patients receiving Janumet in combination with a sulphonylurea or with insulin may be at risk for hypoglycaemia. Therefore, a reduction in the dose of the sulphonylurea or insulin may be necessary.

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 ofthese 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, Janumet should be discontinued, other potential causes of the event should be assessed, and alternative treatment for diabetes should be instituted

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

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 contra-indicated 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 interaction

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. Co-administration of Digoxin and Sitagliptin may slightly increase

the mean peak drug concentration of Digoxin. But no dosage adjustment of digoxin or Sitagliptin is recommended.

Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

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.

4.6. Pregnancy, fertility and lactation

Pregnancy:
It should not be used during pregnancy. If a patient wishes 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
No studies in lactating animals have been conducted with the combined active substances of this medicinal product. In studies performed with the individual active substances, both sitagliptin and metformin are excreted in the milk of lactating rats. Metformin is excreted in human milk in small amounts. It is not known whether sitagliptin is excreted in human milk. Janumet must therefore not be used in women who are breast-feeding .

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

4.7. Effects on ability to drive and use machines

Silinor M 50/500 mg 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.

4.8 Undesirable effects

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

Description of selected adverse reactions
Sitagliptin

In monotherapy studies of sitagliptin 100 mg once daily alone compared to placebo, adverse reactions reported were headache, hypoglycaemia, constipation, and dizziness.
Among these patients, adverse events reported regardless of causal relationship to medicinal product occurring in at least 5 % included upper respiratory tract infection and nasopharyngitis. In addition, osteoarthritis and pain in extremity were reported with frequency uncommon (> 0.5 % higher among sitagliptin users than that in the control group).

Metformin
Gastrointestinal symptoms were reported very commonly in clinical studies and post-marketing use of metformin. Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases. Additional adverse reactions associated with metformin include metallic taste (common); lactic acidosis, liver function disorders, hepatitis, urticaria, erythema, and pruritus (very rare).

4.9 Overdose

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. 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 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.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 hemodialysis. 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 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.

5.0. Pharmacological Properties
5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs, ATC code: A10BD07

Silinor M Tablet 50/500 combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Sitagliptin

Mechanism of action

Sitagliptin phosphate 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 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 antihyperglycaemic 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 utilization
- 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 Pharmacokinetic properties

Silinor M 50/1000

A bioequivalence study in healthy subjects demonstrated that the Silinor M 50/500 (sitagliptin/metformin hydrochloride) combination tablets are bioequivalent to co-administration of sitagliptin phosphate and metformin hydrochloride as individual tablets.

The following statements reflect the pharmacokinetic properties of the individual active substances of Silinor M 50/1000.

Sitagliptin

Absorption

Following oral administration of a 100-mg 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 8.52 M/hr, C_{max} was 950 nM. 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.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner).

Distribution

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

Biotransformation

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 [^{14}C]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 [^{14}C]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 $t_{½}$ following a 100-mg oral dose of sitagliptin was approximately
12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The renal clearance was approximately 350 mL/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=160 □M) or p-glycoprotein (up to 250 □M) 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, T_{max} is reached in 2.5 h. Absolute bioavailability of a 500 mg 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 24-48 h and are generally less than 1 µg/mL. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 µg/mL, even at maximum doses.
Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC and a 35 min 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 – 276 L.

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

Elimination
Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. 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 Silinor M.
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.

6.0 Pharmaceutical Particulars

6.1. List of excipients

-Microcrystalline Cellulose (Type 101)
-Maize Starch
-Povidone (PVP K 30)
-Sodium Starch Glycolate
-Sodium Lauryl Sulphate
-Magnesium Stearate
-Colloidal Anhydrous Silica
-Instacoat Aqua-III Brown A03R00114
-Purified Water

6.2 Incompatibilities

None

6.3 Shelf life

2 years (24 months)

6.4. Special Precaution for storage

Store at temperature not exceeding 30°C in a dry place. Protect from light & moisture.

6.5. Nature and contents of container

. Each blister contains 8 tablets and inner each carton contains 3 blisters i.e. (3 X 8's).

6.6 Special precautions for disposal and other handling

No special requirements

6. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
Healthcare Pharmaceuticals Limited
Address: Nasir Trade Center (Level 9 & 14), 89- Bir Uttam CR Datta Road, Banglamotor, Dhaka-1205
Country: Bangladesh.

Manufacturing site address:
Company name: Healthcare Pharmaceuticals Limited
Address: Gazariapara, Rajendrapur, Gazipur-1703,
Country: Bangladesh

7. Marketing authorization number
CTD10277

8. Date of first registration
20/07/2023

9. Date of revision of the text:
17/09/2023

10. Dosimetry:
Not Applicable

11. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable