- **Summary of Product Characteristics (SmPC)**

1. Name of the medicinal product

(a) Product Name: Linajen-M 2.5/500 Tablet

(b) Strength: Linagliptin 2.5 mg & Metformin Hydrochloride 500 mg per tablet

(c) Pharmaceutical Dosage Form: Oral Tablet

2. Qualitative and Quantitative Composition

- Linagliptin INN
- Metformin Hydrochloride BP

Each tablet contains Linagliptin 2.5 mg & Metformin Hydrochloride 500 mg

3. Pharmaceutical Form

Light orange colored, caplet shaped, standard bi-convex film coated tablet having both sides plain surface.

4. Clinical Particulars

4.1 Therapeutic Indications

Linajen-M 2.5/500 tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both Linagliptin and Metformin is appropriate.

4.2 Posology and method of administration

Posology

Dosage and Administration

Linajen-M should be given twice daily with meals. Dose escalation should be gradual to reduce the gastrointestinal (GI) side effects associated with Metformin use. For available dosage forms and strengths.

Recommended starting dose:

• In patients currently not treated with Metformin, initiate treatment with 2.5 mg Linagliptin/500 mg Metformin Hydrochloride twice daily.

• In patients already treated with Metformin, start with 2.5 mg Linagliptin and the current dose of Metformin taken at each of the two daily meals (e.g., a patient on Metformin 500 mg twice daily would be started on 2.5 mg Linagliptin/500 mg Metformin Hydrochloride twice daily with meals).

• Patients already treated with Linagliptin and Metformin individual components may be switched to Linajen-M containing the same doses of each component.

• No studies have been performed specifically examining the safety and efficacy of Linajen-M in patients previously treated with other oral antihyperglycemic agents and switched to Linajen-M. Any change in therapy of type 2 diabetes mellitus should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin when Linajen-M is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia.

4.3 Contraindications

Linajen-M is contraindicated in patients with:

• Renal impairment (e.g., serum creatinine ≥1.5 mg/dL for men, ≥1.4 mg/dL for women, or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction and septicemia.

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

• A history of hypersensitivity reaction to Linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity.

• Hypersensitivity to Metformin

4.4 Special warning and precautions for use

Lactic acidosis: Warn against excessive alcohol use. Linajen-M is not recommended in hepatic impairment or hypoxic states and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annually thereafter.

• There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue Linajen-M.

• Temporarily discontinue Linajen-M in patients undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures necessitating restricted intake of food and fluids.

• Hypoglycemia: When used with an insulin secretagogue (e.g.sulfonylurea or insulin) consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

• There have been postmarketing reports of serious hypersensitivity reactions in patients treated with Linagliptin (one of the components of Linajen-M) including anaphylaxis, angioedema, and exfoliative skin conditions. In such cases, promptly discontinue Linajen-M, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for
diabetes.

• Vitamin B12 deficiency: Metformin may lower vitamin B12 levels. Monitor hematologic parameters annually.

• Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

• Macrovascular outcomes: No conclusive evidence of macrovascular risk reduction with Linajen-M or any other antidiabetic drug.

4.5 Interaction with other medicinal products and other forms of interactions

Cationic Drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with Metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of Linajen-M and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with Linajen-M, as the risk of lactic acidosis may increase.

Drug Interactions with Linagliptin

Inducers of P-glycoprotein and CYP3A4 Enzymes: Rifampin decreased Linagliptin exposure, suggesting that the efficacy of Linagliptin may be reduced when administered in combination with

a strong P-gp inducer or CYP 3A4 inducer. As Linajen-M is a fixed-dose combination of Linagliptin and Metformin, use of alternative treatments (not containing Linagliptin) is strongly recommended when concomitant treatment with a strong P-gp or CYP 3A4 inducer is necessary.

Drugs Affecting Glycemic Control

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 Linajen-M, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving Linajen-M, the patient should be observed closely for hypoglycemia.

4.6 Fertility, Pregnancy and lactation

Pregnancy

US-FDA Pregnancy Category B

There are no adequate and well controlled studies in pregnant women or its individual components, and some clinical data is available for Metformin which indicate that the risk for major malformations was not increased when Metformin is taken during the first trimester in pregnancy. In addition, metformin was not associated with increased perinatal complications. Nevertheless, because these clinical data cannot rule out the possibility of harm, Linajen-M should be used during pregnancy only if clearly needed. Linajen-M was not teratogenic when administered to Wistar Han rats during the period of organogenesis at doses similar to clinical exposure. At higher maternally toxic doses (9 and 23 times the clinical dose based on exposure), the metformin component of the combination was associated with an increased incidence of fetal rib and scapula malformations.

Nursing Mothers

No studies in lactating animals have been conducted with the combined components of Linajen-M.

Fertility

The effect on human fertility has not been studied. No adverse effects of linagliptin on fertility were observed in male or female rats.

4.7 Effects on ability to drive and use machine

Linajen-M has no or negligible influence on the ability to drive and use machines. However, patients should be alerted to the risk of hypoglycaemia when Linajen-M is used in combination with other anti-diabetic medicinal products known to cause hypoglycaemia (e.g. sulphonylureas).

4.8 Undesirable effects

Summary of the safety profile

The safety of linagliptin 2.5 mg twice daily (or its bioequivalent of 5 mg once daily) in combination with metformin has been evaluated in over 6800 patients with type 2 diabetes mellitus. In placebo-controlled studies, more than 1800 patients were treated with the therapeutic dose of either 2.5 mg linagliptin twice daily (or its bioequivalent of 5 mg linagliptin once daily) in combination with metformin for ≥ 12/24 weeks.

In the pooled analysis of the seven placebo-controlled trials, the overall incidence of adverse events in patients treated with placebo and metformin was comparable to that seen with linagliptin 2.5 mg and metformin (54.3 and 49.0%). Discontinuation of therapy due to adverse events was comparable in patients who received placebo and metformin to patients treated with linagliptin and metformin (3.8% and 2.9%).

The most frequently reported adverse reaction for linagliptin plus metformin was diarrhoea (1.6%) with a comparable rate on metformin plus placebo (2.4%).

Hypoglycaemia may occur when Linajen-M is administered together with sulphonylurea (≥ 1 case per 10 patients).

Tabulated list of adverse reactions

Adverse reactions reported in all clinical trials with the linagliptin+metformin combination or the use of the monocomponents (linagliptin or metformin) in clinical trials or from post-marketing experience are shown below according to system organ class. Adverse reactions previously reported with one of the individual active substances may be potential adverse reactions with Linajen-M, even if not observed in clinical trials with this medicinal product.

The adverse reactions are listed 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), or very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table 2: Adverse reactions reported in patients who received linagliptin+metformin alone (as mono-components or in combination) or as add-on to other anti-diabetic therapies in clinical trial and from post-marketing experience.

System organ class Adverse reaction	**Frequency of adverse reaction**
Infections and infestations	
Nasopharyngitis	uncommon
Immune system disorders	
Hypersensitivity (e.g. bronchial hyperreactivity)	uncommon
Metabolism and nutrition disorders	
Hypoglycaemia [1]	very common
Lactic acidosis [§]	very rare
Vitamin B_{12} deficiency [§]	very rare
Nervous system disorders	
Taste disturbance [§]	common
Respiratory, thoracic and mediastinal disorders	
Cough	uncommon
Gastrointestinal disorders	
Decreased appetite	uncommon
Diarrhoea	common
Nausea	common
Pancreatitis	rare[#]
Vomiting	uncommon
Constipation [2]	uncommon
Abdominal pain [§]	very common
Hepatobiliary disorders	
Liver function disorders [2]	uncommon

Hepatitis §	very rare
Skin and subcutaneous tissue disorders	
Angioedema	rare
Urticaria	rare
Erythema§	very rare
Rash	uncommon
Pruritus	uncommon
Bullous pemphigoid	rare#
Investigations	
Amylase increased	uncommon
Lipase increased*	common

* Based on lipase elevations >3xULN observed in clinical trials

Based on *Linagliptin cardiovascular and renal safety study.*

Description of selected adverse reactions

Hypoglycaemia

In one study linagliptin was given as add-on to metformin plus sulphonylurea. When linagliptin and metformin were administered in combination with a sulphonylurea, hypoglycaemia was the most frequently reported adverse event (linagliptin plus metformin plus sulphonylurea 23.9% and 16.0% in placebo plus metformin plus sulphonylurea).

When linagliptin and metformin were administered in combination with insulin, hypoglycaemia was the most frequently reported adverse event, but occurred at comparable rate when placebo and metformin were combined with insulin (linagliptin plus metformin plus insulin 29.5% and 30.9% in the placebo plus metformin plus insulin group) with a low rate of severe (requiring assistance) episodes (1.5% and 0.9%).

Other adverse reactions

Gastrointestinal disorders such as, nausea, vomiting, diarrhoea and decreased appetite and abdominal pain occur most frequently during initiation of therapy with Linajen-M or metformin hydrochloride and resolve spontaneously in most cases. For prevention, it is recommended that Linajen-M be taken during or after meals. A slow increase in dose of metformin hydrochloride may also improve gastrointestinal tolerability.

Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B_{12} deficiency (e.g. megaloblastic anaemia).

4.9 Management of Overdose

In the event of an overdose with Linajen-M, employ the usual supportive measures (e.g. remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of Linagliptin by hemodialysis or peritoneal dialysis is unlikely.

However, Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated metformin from patients in whom Linajen-M overdosage is suspected.

Linagliptin

During controlled clinical trials in healthy subjects, with single doses of up to 600 mg of Linagliptin (equivalent to 120 times the recommended daily dose), there were no dose-related clinical adverse drug reactions. There is no experience with doses above 600 mg in humans.

Metformin

Overdose of Metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of Metformin overdose cases.

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, *ATC code:* A10BD11

Pharmacodynamics

Linagliptin

Linagliptin binds to DPP-4 in a reversible manner and increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion, thus resulting in a better regulation of the glucose homeostasis. Linagliptin binds selectively to DPP-4 and selectively inhibits DPP-4, but not DPP-8 or DPP-9 activity in vitro at concentrations approximating therapeutic exposures.

Metformin

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike SUs, Metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) and does not cause hyperinsulinemia.

With Metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.2 Pharmacokinetic Properties

Linajen-M

The results of a bioequivalence study in healthy subjects demonstrated that Linajen-M (Linagliptin/Metformin Hydrochloride) 2.5 mg/500 mg, 2.5 mg/850 and 2.5 mg/1000 mg combination tablets are bioequivalent to coadministration of corresponding doses of Linagliptin and Metformin as individual tablets. There was no change in Metformin AUC; however, mean peak serum concentration of Metformin was decreased by 18% when administered with food. A delayed time-to-peak serum concentrations by 2 hours was observed for Metformin under fed conditions. These changes are not likely to be clinically significant.

Absorption

Linagliptin

The absolute bioavailability of Linagliptin is approximately 30%. Following oral administration, plasma concentrations of Linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of Linagliptin to DPP-4. However, the prolonged

elimination does not contribute to the accumulation of the drug. The effective half-life for accumulation of Linagliptin, as determined from oral administration of multiple doses of Linagliptin 5 mg, is approximately 12 hours. After once-daily dosing, steady state plasma concentrations of Linagliptin 5 mg are reached by the third dose, and Cmax and AUC increased by a factor of 1.3 at steady-state compared with the first dose. Plasma AUC of Linagliptin increased in a less than dose-proportional manner in the dose range of 1 to 10 mg. The pharmacokinetics of Linagliptin is similar in healthy subjects and in patients with type 2 diabetes.

Metformin

The absolute bioavailability of a Metformin Hydrochloride 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of Metformin tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination

Distribution

Linagliptin

The mean apparent volume of distribution at steady state following a single intravenous dose of Linagliptin 5 mg to healthy subjects is approximately 1110 L, indicating that Linagliptin extensively distributes to the tissues. Plasma protein binding of Linagliptin is concentration-dependent decreasing from about 99% at 1 nmol/L to 75% to 89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of Linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of Linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Metformin

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

24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials of Metformin, maximum Metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Biotransformation

Linagliptin

Following oral administration, the majority (about 90%) of Linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed Linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to Linagliptin.

Metformin

Intravenous single-dose studies in normal subjects demonstrate that Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Elimination

Linagliptin

Following administration of an oral [14C] Linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 mL/min.

Metformin

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of Metformin elimination. 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.

Characteristics in elderly patients

Linagliptin is minimally excreted by the kidney; however, Metformin is substantially excreted by the kidney. Considering that aging can be associated with reduced renal function, Linajen-M should be used with caution as age increases.

5.3 Preclinical Safety Data

Linagliptin plus metformin

General toxicity studies in rats for up to 13 weeks were performed with the co-administration of linagliptin and metformin. The only observed interaction between linagliptin and metformin was a

reduction of body weight gain. No other additive toxicity caused by the combination of linagliptin and metformin was observed at AUC exposure levels up to 2 and 23 times human exposure, respectively.

An embryofetal development study in pregnant rats did not indicate a teratogenic effect attributed to the co-administration of linagliptin and metformin at AUC exposure levels up to 4 and 30 times human exposure, respectively.

Linagliptin

Liver, kidneys and gastrointestinal tract are the principal target organs of toxicity in mice and rats at repeat doses of linagliptin of more than 300 times the human exposure.

In rats, effects on reproductive organs, thyroid and the lymphoid organs were seen at more than 1500 times human exposure. Strong pseudo-allergic reactions were observed in dogs at medium doses, secondarily causing cardiovascular changes, which were considered dog-specific. Liver, kidneys, stomach, reproductive organs, thymus, spleen, and lymph nodes were target organs of toxicity in Cynomolgus monkeys at more than 450 times human exposure. At more than 100 times human exposure, irritation of the stomach was the major finding in these monkeys.

Linagliptin and its main metabolite did not show a genotoxic potential.

Oral 2 year carcinogenicity studies in rats and mice revealed no evidence of carcinogenicity in rats or male mice. A significantly higher incidence of malignant lymphomas only in female mice at the highest dose (> 200 times human exposure) is not considered relevant for humans (explanation: non-treatment related but due to highly variable background incidence). Based on these studies there is no concern for carcinogenicity in humans.

The NOAEL for fertility, early embryonic development and teratogenicity in rats was set at > 900 times the human exposure. The NOAEL for maternal-, embryo-fetal-, and offspring toxicity in rats was 49 times human exposure. No teratogenic effects were observed in rabbits at > 1,000 times human exposure. A NOAEL of 78 times human exposure was derived for embryo-fetal toxicity in rabbits, and for maternal toxicity the NOAEL was 2.1 times human exposure. Therefore, it is considered unlikely that linagliptin affects reproduction at therapeutic exposures in humans.

Metformin

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. Pharmaceutical Particulars

6.1 List of excipients

As per formulation

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store in a dry place below 30^0 C protected from light. Keep out of reach of children.

6.5 Nature and contents of container

From the results of the stability study, it is confirmed that Linagliptin 2.5 mg and Metformin Hydrochloride 500 mg combination tablet is stable for 2 years and packed in Alu- Alu Blister pack. This Alu- Alu Blister packs are further packed in secondary packs (Inner Carton) & finally in paperboard Master carton for providing extra protection.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. **Pack Size:** Each packs contains 3x10's tablets in Alu-Alu blister pack.

8. Marketing Authorization Holder (Applicant/Manufacturer)

Name: Popular Pharmaceuticals Ltd.

Factory Address: 164, Tongi Industrial Area, Tongi, Gazipur-1711, Bangladesh.