1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

====*Attached*===

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

CO-DILOPRIL (Amlodipine and Lisinopril Tablets)

2. Qualitative and quantitative composition

Each film coated tablet contains:
Amlodipine Besylate USP
Eq. to Amlodipine 5 mg
Lisinopril USP
Eq. to Lisinopril anhydrous 5 mg

3. Pharmaceutical form

Oral solid dosage form

4. Clinical particulars

4.1 Therapeutic indications

CO-DILOPRIL is indicated in the treatment of mild to moderate hypertension. It is also indicated in hypertension not responding to monotherapy with ACE inhibitors or calcium antagonists. It may also be substituted for the titrated doses of the individual components.

Hypertension
Treatment of hypertension.

Coronary Artery Disease (CAD)
Chronic Stable Angina

Heart failure
Treatment of symptomatic heart failure.
Acute myocardial infarction
Short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction.
Renal complications of diabetes mellitus
Treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy (see section 5.1)

4.2 Posology and method of administration

The usual initial dosage is one tablet daily. If blood pressure control is inadequate after a week or two, the dose may be increased to two tablets daily. The dosage howevershould be individualized.

4.3 Contraindications

Hypersensitivity to either component, history of angioedema related to previous treatment with an ACE inhibitor, in patients with hereditary or idiopathic angioedema and in pregnancy.

4.4 Special warnings and precautions for use

Diuretics: Patients on diuretics may occasionally experience an excessive reduction of blood pressure after initiation of therapy with this combination. The possibility of hypotensive effects can be minimized by either discontinuing the combination or increasing the salt intake priorto initiation of treatment

Agents Increasing serum potassium: lisinopril attenuates potassium loss caused by thiazide-type diuretics. If concomitant use of these agents is indicated, they should be used with caution, and with frequent monitoring of serum potassium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. CO-DILOPRIL and lithium should be Co-administered with caution, and Frequent monitoring of serum lithium levels is recommended.

NSAIDs: In some patients with compromised renal function who are being treated with non-steroidal anti inflammatory drugs, the co-administration of lisinopril may result in a further deterioration of renal function. These effects are usually reversible. NSAIDs blunt the antihypertensive effect of ACE inhibitors including lisinopril. This should be given consideration in patients taking NSAIDs concomitantly with CO-DILOPRIL. Indomethacin may reduce the antihypertensive efficacy of lisinopril.

4.5 Interaction with other medicinal products and other forms of interaction
Increased Angina and/or Myocardial Infarction

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute

Interaction with other medicinal products and other forms of interaction myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Amlodipine should be administered with caution to patients with low cardiac reserve.

Patients with heart failure

Patients with cardiac failure should be treated with caution. In a long-term study including patients suffering from severe heart failure (NYHA grade m and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group, but this was not indicating an aggravation of the heart failure.

Use in patients with impaired hepatic function.

The half-life of amlodipine is prolonged in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be administered with caution, in these patients.

Use in elderly patients

In the elderly, increase of the dosage should take place with care.

Use in children

Amlodipine should not be given to children due to insufficient clinical experience.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use of pregnancy & breastfeeding The safety of Amlodipine in human pregnancy has not been established Amlodipine should only be given during pregnency when the benefit outweighs the risk. The use of Amlodipine is not recommended during breastfeeding. Some mothers appear to excrete amounts of Amlodipine in milk that might affect some safety data become available, an alternate drug may be preferred.

Lisinopril can interact with the following drugs or groups of drugs:

• Diuretics:

When a diuretic is added to the therapy of a patient receiving lisinopril the antihypertensive effect is usually additive.

Patients already on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure when lisinopril is added. The possibility of symptomatic hypotension with lisinopril can be minimised by discontinuing the diuretic prior to initiation of treatment with lisinopril (see section 4.4).

• Potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes:

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes. The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium. If lisinopril is given with a potassium-losing diuretic, diuretic - induced hypokalaemia may be ameliorated.

• Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Use of lisinopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

• Non steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid ≥ 3G/day:

Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated.

• Other antihypertensive agents:

Concomitant use of these agents may increase the hypotensive effects of lisinopril. Concomitant use with glyceryl trinitrate and other nitrates, or other vasodilators, may further reduce blood pressure.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

• Tricyclic antidepressants / anaesthetics / muscle relaxants:

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants, antipsychotics or muscle relaxants with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

• Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

• Antidiabetics:

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicinal products (insulins, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

• Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:

Lisinopril may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates.

• Gold

Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

• *mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)*

Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.4).

• *Co-trimoxazole (trimethoprim/sulfamethoxazole)*

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia

4.6 Pregnancy and lactation

It is recommended that the combination should be avoided in pregnancy & breast feeding unless essential as it may adversely affect fetal and neonatal blood pressure control and renal function.

4.7 Effects on ability to drive and use machines

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

The combination of amlodipine and lisinopril is well tolerated. Angioneurotic oedema has been reported with ACE inhibitors. In such cases the combination should be discontinued immediately. Other side effects include nausea, headache, dizziness, cough, diarrhoea, fatigue , rash, oedema, flushing, palpitations, chest pain and asthenia. Increase in blood urea, serum potassium and creatinine may occur.

4.9 Overdose

The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. Unabsorbed drugs may be removed by gastric lavage or administration of activated charcoal. Symptomatic treatment is suggested.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lisinopril: Angiotensin converting enzyme inhibitors, ATC code: C09A A03

Amlodipine Besylate: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC Code: C08CA01

Amlodipine

Amlodipine is a dihydropyridine calcium antagonist (calcium Ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx ocross cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect Amlodipine Is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Hemodynamics: Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

With chronic once daily oral administration, anti hypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105 -114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90- 104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when coadministered with beta-blockers to man. Similar findings, however, have been observed in normal or well- compensated patients with heart failure with agents possessing significant negative inotropic effects.

Electrophysiologic Effects: Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or men. In clinical studies in which amlodipine was administered in combination with beta- blockers to patients with hypertension, no adverse effects on electro cardiographic porameters were observed

Lisinopril

Lisinopril inhibits angiotensin converting enzyme (ACE) in human subjects and animals. The beneficial effects of lisinopril in hypertension appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased vasopressor activity and to decrease aldosterone secretion. The latter decrease may result in a small increase of serum potassium. ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low-renin hypertension. Although lisinopril was anti hypertensive in all races studied, Black hypertensive patients (usually a low-renin hypertensive population) had a smaller average responsetomonotherapythannon-Blackpatients.

Administration of lisinopril to patients with hypertension results in a reduction of supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is usually not observed although it can occur and should be anticipated in volume and/or salt-depleted patients. When given together with thiazide-type diuretics, the blood

pressure lowering effects of the two drugs are approximately additive.
In most patients studied , onset of anti hypertensive activity was seen at one hour after oral administration of an individual dose of lisinopril, with peak reduction of blood pressure achieved by six hours. Although an anti hypertensive effect was observed 24 hours after dosing with recommended single daily doses, the effect was more consistent and the mean effect was considerably larger in some studies with doses of 20 mg or more than with lower doses. However, at all doses studied, the mean antihypertensive effect was substantially smaller 24 hours after dosing than it was six hours after dosing. In some patients achievement of optimal blood pressure reduction may require two to four weeks of therapy.
The anti hypertensive effects of lisinopril are maintained during long -term therapy. Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure or a significant increase in blood pressure compared to pretreatment levels.
Lisinopril had similar effectiveness and adverse effects in younger and older (>65 years) patients. It was less effective in Blacks than in Caucasians.
In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate.
In patients with renovascular hypertension lisinopril has been shown to be well tolerated and effective incontrolling blood pressure.
The dose-dependent anti hypertensive effect of lisinopril was consistent across several demographic subgroups:age, Tanner stage, gender and race.

5.2 Pharmacokinetic properties

Amlodipine

After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine is not altered by the presence of food.
Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine . Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.
The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.
Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose maybe required. A similar increase In AUC was observed in patients with moderate to severe heart failure.

Pediatric Patients: Sixty-two hypertensive patients aged to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

Lisinopril

Adult Patients: Following oral administration of lisinopril, peak serum concentrations of lisinopril

occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Declining serum concentrations exhibit a prolonged terminal Phase, which does not contribute to drug accumulation. This Terminal Phase probably represents saturable binding to ACE and Is not proportional to dose, lisinopril does not appear to be bound to other serum proteins.

Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25 percent, with large intersubject variability (6-60 percent) at all doses tested (5-80 mg). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract. The absolute bioavailability of lisinopril is reduced to about 16 percent in patients with stable NYHA Class II-IV congestive heart failure, and the volume of distribution appears to be slightly smaller than that in normal subjects.

The oral bioavailability of lisinopril in patients with acute myocardial infarction is similar to that in healthy volunteers. Upon multiple dosing, lisinopril exhibits an effective half-life of accumulation of 12 hours.

Impaired renal function decreases elimination of lisinopril .which is excreted principally through the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/min. above this glomerular filtration rate, the elimination half-life is little changed. With greater impairment, however, peak and trough lisinopril levels increase, time to peak concentration increase s and time to attain steady state is prolonged. Older patients, on average, have (approximately doubled) higher blood levels and area under the plasma concentration time curve (AUC) than younger patients, lisinopril can be removed by hemodialysis.

Studies in rats indicate that lisinopril crosses the blood- brain barrier poorly. Multiple doses of lisinopril in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of 14 lisinopril. By whole body autoradiography, radioactivity was found in the placenta following administration of labeled drug to pregnant rats, but none was found in the fetuses.

Pediatric Patients: The pharmacokinetics of lisinopril were studied in 29 pediatric hypertensive patients between 6 years and 16 years with glomerular filtration rate >30 mL/min/1-73 m2. After doses of 0.1 to 0.2 mg/kg, steady state peak plasma concentrations of lisinopril occurred within 6 hours and the extent of absorption based on urinary recovery was about 28 %. These values are similar to those obtained previously in adults. The typical value of lisinopril oral clearance (systemic clearance/absolute bioavailability in a child weighing 30 kg is 10 L/h, which increases in proportion to renal function.

5.3 Preclinical properties

Amlodipine Besylate

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on

a mg/m basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells. Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.
*Based on patient weight of 50 kg

Lisinopril

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull.

Foetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported.

These developmental anomalies are thought to be partly due to a direct action of ACE inhibitors on the foetal renin -angiotensin system and partly due to ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus.

6. Pharmaceutical particulars

6.1 List of excipients
Mannitol, Dibasic Calcium Phosphate, Microcrystalline Cellulose, Pregelatinized Starch, Magnesium Stearate, Croscarmellose Sodium, Colloidal Silicon Dioxide, Colour Opadry white (containing Titanium Dioxide USP), Colour Tartrazine Lake and Purified water

6.2 Incompatibilities
None

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store in the original package below 30 °C.
KEEP OUTOF REACH OF CHILDREN.

6.5 Nature and contents of container

10 tablets packed in Alu-Alu Blister; Such 3 Blister packed in a carton with insert.

6.6 Special precautions for disposal and other handling
Not applicable.

7. Manufactured By
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8. Marketing authorisation number(s)
----A4 -4466----

9. Date of first authorisation/renewal of the authorisation
----December, 2022