Summary of Product Characteristics

1. Name of the Medical Product
Amlogood At 10

2. Qualitative & Quantitative Composition:
Each film coated tablet contains:
Amlodipine Besylate USP
Eq. to Amlodipine .....5 mg
Atorvastatin calcium USP
Eq. to Atorvastatin.....20 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form:
Tablet

4. Clinical Particulars
4.1 Therapeutic Indications:
The amlodipine/atorvastatin combination product (henceforth in this document termed "amlodipine/atorvastatin") is indicated for the following patient populations:
1. Patients at increased cardiovascular risk due to the presence of the two modifiable risk factors hypertension and dyslipidemia; and /or
2. Patients at increased cardiovascular risk due to the presence of symptomatic Coronary Heart Disease (CHD) expressed as angina with the additional modifiable risk factor of dyslipidemia; and/or 3. Prevention of cardiovascular complications in hypertensive patients (see below - Prevention of Cardiovascular Complications). In these patients with multiple cardiovascular risk factors, amlodipine/atorvastatin is indicated for:
Hypertension
The amlodipine component is indicated for the first-line treatment of hypertension and can be used as the sole agent to control blood pressure (BP) in the majority of patients. Patients not adequately controlled on a single antihypertensive agent (other than amlodipine) may benefit from the addition of the amlodipine component of amlodipine/atorvastatin, in the same manner as they would benefit from the addition of amlodipine alone. Amlodipine is also indicated to reduce the risk of fatal CHD and non-fatal myocardial infarction (MI), and to reduce the risk of stroke.
Coronary Artery Disease
The amlodipine component is indicated to reduce the risk of coronary revascularization procedures and the need for hospitalization due to angina in patients with coronary artery disease (CAD).
Chronic Stable Angina
The amlodipine component is indicated for the first-line treatment of myocardial ischemia, whether due to fixed obstruction (stable angina) and/or vasospasm/vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature. Amlodipine/atorvastatin may be used where the clinical presentation suggests a possible vasospastic/vasoconstrictive component but where vasospasm/vasoconstriction has not been confirmed. Amlodipine/atorvastatin may

be used alone or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta blockers.
Dyslipidemia
The atorvastatin component is indicated as an adjunct to diet for the treatment of patients with elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and triglycerides (TG) and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial hypercholesterolemia), combined (mixed) hyperlipidemia (Fredrickson Types IIa and IIb), elevated serum TG levels (Fredrickson Type IV), and in patients with dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet.
The atorvastatin component is also indicated for the reduction of total C and LDL-C in patients with homozygous familial hypercholesterolemia (FH).
Prevention of Cardiovascular Complications
In patients without clinically evident cardiovascular disease (CVD), and with or without dyslipidemia, but with multiple risk factors for CHD such as smoking, hypertension, diabetes, low HDL-C, or a family history of early CHD, atorvastatin is indicated to:

- Reduce the risk of fatal CHD and non-fatal MI
- Reduce the risk of stroke
- Reduce the risk of revascularization procedures and angina pectoris In patients with clinically evident CHD, atorvastatin is indicated to:
- Reduce the risk of non-fatal MI
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for congestive heart failure (CHF)
- Reduce the risk of angina

Pediatric Patients (10-17 years of age)
Atorvastatin is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous FH if after an adequate trial of diet therapy the following findings are present: a. LDL-C remains □190 mg/dL or
b. LDL-C remains □160 mg/dL and

- There is a positive family history of premature CVD or
- Two or more other CVD risk factors are present in the pediatric patient

4.2 Posology and Method of administration:
Posology
General Considerations
Amlodipine/atorvastatin is a combination product targeting concomitant cardiovascular conditions, hypertension/angina and dyslipidemia.
The dosage range for amlodipine/atorvastatin is 5 mg/10 mg to a maximum dose of 10 mg/80 mg once daily. The starting dose and maintenance dose should be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and dyslipidemia. Current treatment guidelines should be consulted to establish treatment goals for patients based on their baseline characteristics. Doses may be taken at any time of day with or without food.
As a component of multiple risk factor intervention, amlodipine/atorvastatin should be used in addition to non-pharmacological measures, including an appropriate diet,

exercise and weight reduction in obese patients, smoking cessation, and to treat underlying medical problems, when the response to these measures have been inadequate.
Following initiation and/or titration of amlodipine/atorvastatin, lipid levels should be analyzed and BP measured within 2 to 4 weeks, and dosage of amlodipine and atorvastatin components should be adjusted accordingly. Titration for BP response may proceed more rapidly if clinically warranted.
Initial Therapy
Amlodipine/atorvastatin may be used to initiate treatment in patients with hyperlipidemia and either hypertension or angina. The recommended starting dose of amlodipine/atorvastatin should be based on the appropriate combination of recommendations for the amlodipine and atorvastatin components considered separately. The maximum dose of the amlodipine component of amlodipine/atorvastatin is 10 mg once daily. The maximum dose of the atorvastatin component of amlodipine/atorvastatin is 80 mg once daily.
Substitution Therapy
Amlodipine/atorvastatin may be substituted for its individually titrated components. Patients may be given the equivalent dose of amlodipine/atorvastatin or a dose of amlodipine/atorvastatin with increased amounts of amlodipine, atorvastatin or both for additional antianginal effects, BP lowering, or lipid-lowering effect.

4.3 Contraindications:
Amlodipine/atorvastatin is contraindicated in patients who:
1. Have known hypersensitivity to dihydropyridines,* amlodipine, atorvastatin, or any component of this medication,
2. Have active liver disease or unexplained persistent elevations of serum transaminases >3 x the upper limit of normal [ULN],
3. Are pregnant, breast-feeding, or of childbearing potential who are not using adequate contraceptive measures. Amlodipine/atorvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards to the fetus. * Amlodipine is a dihydropyridine calcium channel blocker.

4.4 Special warnings & precautions for use
Use in Patients with Heart Failure
In a long-term, placebo-controlled study (PRAISE-2) of amlodipine-treated patients with New York Heart Association (NYHA) class III-IV heart failure of nonischemic etiology, amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure as compared to placebo
Use in Patients with Impaired Hepatic Function
Hepatic Effects
As with other lipid-lowering agents of the HMG-CoA reductase inhibitor class, moderate (>3 x ULN) elevations of serum transaminases have been reported following therapy with atorvastatin. Liver function was monitored during pre-marketing as well as post-marketing clinical studies of atorvastatin given at doses of 10 mg, 20 mg, 40 mg and 80 mg.
Persistent increases in serum transaminases (>3 x ULN on two or more occasions) occurred in 0.7% of patients who received atorvastatin in these clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10 mg, 20 mg, 40 mg and 80 mg, respectively. Increases were generally not associated with

jaundice or other clinical signs or symptoms. When the dosage of atorvastatin was reduced, or drug treatment interrupted or discontinued, transaminase levels returned to pre-treatment levels. Most patients continued treatment on a reduced dose of atorvastatin without sequelae.
Amlodipine/atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of amlodipine/atorvastatin.

4.5 Interactions with other medicinal products and other forms of Interactions
Data from a drug-drug interaction study involving 10 mg of amlodipine and 80 mg of atorvastatin in healthy subjects indicate that the pharmacokinetics of amlodipine are not altered when the drugs are co-administered. The effect of amlodipine on the pharmacokinetics of atorvastatin showed no effect on the Cmax: 91% (90% confidence interval [CI]: 80%-103%), but the AUC of atorvastatin increased by 18% (90% CI: 109%-127%) in the presence of amlodipine.
No drug interaction studies have been conducted with amlodipine/atorvastatin and other drugs, although studies have been conducted using the individual amlodipine and atorvastatin components, as described below:
Amlodipine Interactions
Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.
CYP3A4 Inhibitors
Co-administration of a 180 mg daily dose of diltiazem with 5 mg of amlodipine in elderly hypertensive patients (69-87 years of age) resulted in a 57% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers (18-43 years of age) did not significantly change amlodipine systemic exposure (22% increase in AUC). Although the clinical relevance of these findings is uncertain, the pharmacokinetic variations may be more pronounced in the elderly. Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors.
Clarithromycin
Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co-administered with clarithromycin.
CYP3A4 Inducers
There are no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

4.6 Pregnancy and Lactation
Amlodipine/atorvastatin is contraindicated in pregnancy due to the atorvastatin component.2 Women of childbearing potential should use adequate contraceptive measures.
Amlodipine/atorvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards to the fetus.

Amlodipine/atorvastatin is contraindicated while breast-feeding due to the atorvastatin component. It is not known whether atorvastatin is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking amlodipine/atorvastatin should not breast-feed.
Safety of amlodipine in human pregnancy or lactation has not been established. Amlodipine did not demonstrate toxicity in animal reproductive studies other than to delay parturition and prolong labor in rats at a dose level 50 times the maximum recommended dose in humans. There was no effect on the fertility of rats treated with amlodipine

4.7 Effects on ability to drive and use machine*:
Based on the available information on amlodipine and atorvastatin, this medication is unlikely to impair patient's ability to drive or use machinery.

4.8 Undesirable Effects
Combination therapy with amlodipine and atorvastatin has been evaluated for safety in 1092 patients in double-blind, placebo-controlled studies treated for concomitant hypertension and dyslipidemia. In clinical trials, no adverse events peculiar to combination therapy with amlodipine and atorvastatin have been observed. Adverse events have been limited to those that were reported previously with amlodipine and/or atorvastatin (please see respective adverse event experiences below).
In general, combination therapy with amlodipine and atorvastatin was well tolerated. For the most part, adverse events have been mild or moderate in severity. In controlled clinical trials, discontinuation of therapy due to adverse events or laboratory abnormalities was required in 5.1% of patients treated with both amlodipine and atorvastatin compared to 4.0% of patients given placebo.
The following information is based on clinical trials and postmarketing experience with amlodipine and atorvastatin. Amlodipine Experience
Amlodipine is well tolerated. In placebo-controlled clinical trials involving patients with hypertension or angina, the most commonly observed side effects were:

MedDRA System Organ Class	**Undesirable Effects**
Nervous System Disorders	Headache, dizziness, somnolence
Cardiac Disorders	Palpitations
Vascular Disorders	Flushing
Gastrointestinal Disorders	Abdominal pain, nausea
General Disorders and Administration Site Conditions	Oedema, fatigue

In these clinical trials, no pattern of clinically significant laboratory test abnormalities related to amlodipine has been observed. Less commonly observed side effects in marketing experience with amlodipine include:

MedDRA System Organ Class	Undesirable Effects
Blood and Lymphatic System Disorders	Leucopenia, thrombocytopenia
Metabolism and Nutrition Disorders	Hyperglycaemia
Psychiatric Disorders	Insomnia, mood altered
Nervous System Disorders	Hypertonia, hypoaesthesia/paraesthesia, neuropathy peripheral, syncope, dysgeusia, tremor, extrapyramidal disorder
Eye Disorders	Visual impairment
Ear and Labyrinth Disorders	Tinnitus
Vascular Disorders	Hypotension, vasculitis
Respiratory, Thoracic, and Mediastinal Disorders	Cough, dyspnoea, rhinitis
Gastrointestinal Disorders	Change in bowel habits, dry mouth, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting
Skin and Subcutaneous Tissue Disorders	Alopecia, hyperhidrosis, purpura, skin discolouration, urticarial
Musculoskeletal and Connective Tissue Disorders	Arthralgia, back pain, muscle spasms, myalgia
Renal and Urinary Disorders	Pollakiuria, micturition disorder, nocturia
Reproductive System and Breast Disorders	Gynaecomastia, erectile dysfunction
General Disorders and Administration Site Conditions	Asthenia, malaise, pain
Investigations	Weight increased/decreased

Rarely reported events were allergic reactions including pruritus, rash, angioedema, and erythema multiforme.

Hepatitis, jaundice and hepatic enzyme elevations have also been reported very infrequently (mostly consistent with cholestasis). Some cases severe enough to require hospitalization have been reported in association with use of amlodipine. In many instances, causal association is uncertain.

As with other calcium channel blockers, the following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: MI, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain.

Pediatric Patients (Aged 6-17 years)

Amlodipine is well tolerated in children. Adverse events were similar to those seen in adults. In a study of 268 children, the most frequently reported adverse events were:

MedDRA System Organ Class	Undesirable Effects
Nervous System Disorders	Headache, dizziness
Vascular Disorders	Vasodilatation
Respiratory, Thoracic, and Mediastinal Disorders	Epistaxis
Gastrointestinal Disorders	Abdominal pain
General Disorders and Administration Site Conditions	Asthenia

The majority of adverse events were mild or moderate. Severe adverse events (predominantly headache) were experienced by 7.2% with amlodipine 2.5 mg, 4.5% with amlodipine 5 mg, and 4.6% with placebo. The most common cause of discontinuation from the study was uncontrolled hypertension. There were no

discontinuations due to laboratory abnormalities. There was no significant change in heart rate.
Atorvastatin Experience
Atorvastatin is generally well tolerated. Adverse reactions have usually been mild and transient. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 atorvastatin vs. 7311 placebo) patients treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.
The most frequent (□1%) adverse effects that may be associated with atorvastatin therapy, reported in patients participating in placebo-controlled clinical studies include:
Infections and Infestations: nasopharyngitis
Metabolism and nutrition disorders: hyperglycaemia
Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain, epistaxis
Gastrointestinal disorders: diarrhoea, dyspepsia, nausea, flatulence
Musculoskeletal and connective tissue disorders: arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, myalgia, joint swelling
Investigations: liver function test abnormal, blood creatine phosphokinase increased Additional adverse effects reported in atorvastatin placebo-controlled clinical trials include:
Psychiatric disorders: nightmare Eye disorders: vision blurred Ear and labyrinth disorders: tinnitus Gastrointestinal disorders: abdominal discomfort, eructation Hepatobiliary disorders: hepatitis, cholestasis Skin and subcutaneous tissue disorders: urticaria Musculoskeletal and connective tissue disorders: muscle fatigue, neck pain General disorders and administration site conditions: malaise, pyrexia Investigations: white blood cells urine positive Not all effects listed above have been causally associated with atorvastatin therapy.

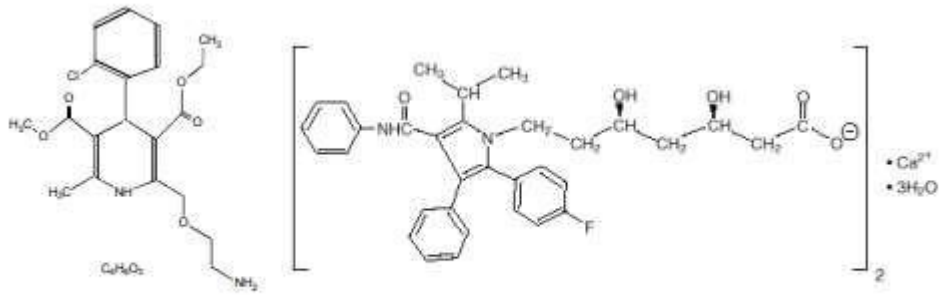
Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9 Overdose:
There is no information on overdosage with amlodipine/atorvastatin in humans. Due to amlodipine's and atorvastatin's extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance amlodipine/atorvastatin clearance
Additional data on amlodipine ingestion suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported. Administration of activated charcoal to healthy volunteers immediately or up to 2 hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and BP, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

5. Pharmacological properties:

5.1 Pharmacodynamic Properties:

Amlodipine/Atorvastatin Pharmacodynamics The amlodipine besylate component of amlodipine/atorvastatin is chemically described as (R.S.) 3-ethyl-5-methyl-2-(2aminoethoxymethyl) - 4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulfonate. Its empirical formula is C20H25CIN2O5•C6H6O3S. The atorvastatin calcium component of amlodipine/atorvastatin is chemically described as [R-(R*, R*)]-2-(4-fluorophenyl)-ß, □-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is (C33H34 FN2O5)2Ca•3H2O. The structural formulae are shown below:



Amlodipine besylate Atorvastatin calcium

Mechanism of Amlodipine/Atorvastatin

Amlodipine/atorvastatin combines two mechanisms of action: the dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) action of amlodipine and the HMGCoA reductase inhibition of atorvastatin. The amlodipine component of

amlodipine/atorvastatin inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The atorvastatin component of amlodipine/atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts HMG-CoA to mevalonate, a precursor of sterols, including cholesterol.

Clinical Studies of Combined Amlodipine and Atorvastatin in Patients with Hypertension and Dyslipidemia

In a double-blind, placebo-controlled study of 1660 patients with comorbid hypertension and dyslipidemia, once-daily treatment with eight-dose combinations of amlodipine and atorvastatin (5/10 mg, 10/10 mg, 5/20 mg, 10/20 mg, 5/40 mg, 10/40 mg, 5/80 mg, or 10/80 mg) was compared vs. amlodipine alone (5 mg or 10 mg), atorvastatin alone (10 mg, 20 mg, 40 mg, or 80 mg), and placebo. In addition to concomitant hypertension and dyslipidemia, 15% of the patients had diabetes mellitus, 22% were smokers and 14% had a positive family history of CVD. At 8 weeks, all eight combination-treatment groups demonstrated statistically significant dose-related reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP) and LDL-C compared to placebo, with no overall modification of effect of either component on SBP, DBP and LDL-C (see table below). Efficacy in Terms of Reduction in Blood Pressure and LDL-C

Efficacy of the Combined Treatments in Reducing Systolic BP[a]						
Parameter/Analysis		ATO[b] 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML[c] 0 mg	Mean change (mmHg)	-3.0	-4.5	-6.2	-6.2	-6.4
	Difference vs. placebo (mmHg)	-	-1.5	-3.2	-3.2	-3.4
AML 5 mg	Mean change (mmHg)	-12.8	-13.7	-15.3	-12.7	-12.2
	Difference vs. placebo (mmHg)	-9.8	-10.7	-12.3	-9.7	-9.2
AML 10 mg	Mean change (mmHg)	-16.2	-15.9	-16.1	-16.3	-17.6
	Difference vs. placebo (mmHg)	-13.2	-12.9	-13.1	-13.3	-14.6

[a] Blood pressure.
[b] Atorvastatin.
[c] Amlodipine.

Amlodipine Pharmacodynamics

Amlodipine is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischemic burden by the following two actions.

1. Amlodipine dilates peripheral arterioles and thus reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina) and blunts smoking-induced coronary vasoconstriction

In patients with hypertension, once-daily dosing provides clinically significant reductions of BP in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once-daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1 mm ST segment depression, and decreases both angina attack frequency and nitroglycerine tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Atorvastatin Pharmacodynamics ‘
Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. In patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia, atorvastatin reduces total-C, LDL-C, and apo B. Atorvastatin also reduces very-lowdensity lipoprotein cholesterol (VLDL-C)(and TG and produces variable increases in HDL-C.
Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.
Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL in patients with homozygous FH, a population that has not normally responded to lipid-lowering medication.
Atorvastatin and some of its metabolites are pharmacologically active in humans. The primary site of action of atorvastatin is the liver, which is the principal site of cholesterol synthesis and LDL-clearance. LDL-C reduction correlates better with drug dose than it does with systemic drug concentration. Individualization of drug dosage should be based on therapeutic response.

5.2 Pharmacokinetics Properties*:
Pharmacokinetics and Metabolism Absorption In studies with amlodipine/atorvastatin Following oral administration of amlodipine/atorvastatin, two distinct peak plasma concentrations were observed. The first, within 1 to 2 hours of administration, is attributable to atorvastatin; the second, between 6 and 12 hours after dosing, is attributable to amlodipine. The rate and extent of absorption (bioavailability) of amlodipine and atorvastatin from amlodipine/atorvastatin are not significantly different from the bioavailability of amlodipine and atorvastatin from coadministration of amlodipine and atorvastatin tablets as assessed by Cmax: 101% (90% CI: 98, 104) and AUC: 100% (90% CI: 97, 103) for the amlodipine component and Cmax: 94% (90% CI: 85, 104) and AUC: 105% (90% CI: 99, 111) for the atorvastatin component, respectively
The bioavailability of the amlodipine component of amlodipine/atorvastatin was not affected under the fed state as assessed by Cmax: 105% (90% CI: 99, 111) and AUC: 101% (90% CI: 97, 105) relative to the fasted state. Although food decreases the rate and extent of absorption of atorvastatin from amlodipine/atorvastatin by approximately 32% and 11%, respectively, as assessed by Cmax: 68% (90% CI 60, 79) and AUC: 89% (90% CI 83, 95) relative to the fasted state, similar reductions in plasma concentrations in the fed state have been seen with atorvastatin taken as monotherapy without reduction in LDL-C effect (see below).
In studies with amlodipine
After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6 to 12 hours post-dose. Absolute bioavailability has been estimated to be between 64% and 80%. The volume of distribution is approximately 21 L/kg. In vitro studies have shown that approximately 97.5% of circulating

amlodipine is bound to plasma proteins. Absorption of amlodipine is unaffected by consumption of food.

In studies with atorvastatin
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption and plasma atorvastatin concentrations increases in proportion to atorvastatin dose. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions. The absolute bioavailability of atorvastatin is approximately 14%, and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic firstpass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared to morning. However, LDL-C reduction is the same regardless of the time of day of drug administration Distribution
In studies with atorvastatin Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is 98% bound to plasma proteins. A red blood cell/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.
Metabolism and Excretion
In studies with amlodipine The terminal plasma elimination half-life is about 35 to 50 hours and is consistent with once daily dosing. Steady-state plasma levels are reached after 7 to 8 days of consecutive dosing. Amlodipine is extensively metabolized by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.
In studies with atorvastatin
Atorvastatin is extensively metabolized to ortho- and para-hydroxylated derivatives and various beta-oxidation products. In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In vitro studies suggest the importance of atorvastatin metabolism by hepatic cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme. In vitro studies also indicate that atorvastatin is a weak inhibitor of cytochrome P450 3A4. Atorvastatin co-administration did not produce a clinically significant effect in plasma concentrations of terfenadine, a compound predominantly metabolized by cytochrome P450 3A4; therefore, it is unlikely that atorvastatin will significantly alter the pharmacokinetics of other cytochrome P450 3A4 substrates (see section 4.5. Interaction with other medicinal products and other forms of interaction). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.
Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.
Atorvastatin is a substrate of the hepatic transporters, OATP1B1 and OATP1B3 transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is

also identified as a substrate of the efflux transporters MDR1 and BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.

5.3 Preclinical safety data

Carcinogenesis

In studies with amlodipine Rats and mice treated with amlodipine in the diet for 2 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/m2 basis) was close to the maximum tolerated dose for mice but not for rats.

In studies with atorvastatin

Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8- to 16-fold higher based on AUC (0-24) values. In a 2-year study in mice, incidences of hepatocellular adenomas in males and hepatocellular carcinomas in females were increased at the maximum dose used, which was 250fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on AUC (0-24).

6. Pharmaceutical particulars:

6.1 List of Excipients:

SR. NO.	INGREDIENTS
1.	Dicalcium Phosphate
2.	Microcrystalline cellulose
3.	Maize Starch
4.	Colloidal silicon dioxide
5.	Sodium Starch Glycolate
6.	Purified Talc
7.	Magnesium Stearate
8.	Ready mix Yellow Coat
9.	*Isopropyl Alcohol
10.	*Methylene Chloride

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

36 months

6.4 Special Precautions for storage:

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container:

10 tablets are packed in ALU-ALU blister, such 3 blisters are packed in one carton with insert coded with batch number, manufacturing date and expiry date.

6.6 Special precautions for disposal:

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder:
ZAIN PHARMA LTD.
Plot No: 209/13741, Colchester Park,
Go-Down No.1, 2, 3, Off Mombasa Road,
Behind Nice And Lovely House,
P.O. Box: 100167-00101, Nairobi,Kenya

Manufacturing Site Address:
ZAIN PHARMA LTD.
Plot No: 209/13741, Colchester Park,
Go-Down No.1, 2, 3, Off Mombasa Road,
Behind Nice And Lovely House,
P.O. Box: 100167-00101, Nairobi,Kenya

8. Marketing Authorization Numbers:
H2025/CTD11870/25350

9. Date of first registration /renewal of the registration:
2025 June 30

10. Date of revision of text:
2025 June 30