Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Edecil (Cilnidipine) 5 mg Tablet
Edecil (Cilnidipine) 10 mg Tablet
Edecil (Cilnidipine) 20 mg Tablet

2. Qualitative and quantitative composition

Edecil -5 mg:
Each film-coated tablet contains Cilnidipine 5 mg.

Excipients with known effects:
Each film-coated tablet contains Mannitol 44.39 mg (as diluent)
Each film-coated tablet contains Sodium Lauryl Sulfate 0.97 mg

Edecil -10 mg:
Each film-coated tablet contains Cilnidipine 10 mg.

Excipients with known effects:
Each film-coated tablet contains Mannitol 44.39 mg (as diluent)
Each film-coated tablet contains Sodium Lauryl Sulfate 0.97 mg

Edecil -20 mg:
Each film-coated tablet contains Cilnidipine 20 mg.

Excipients with known effects:
Each film-coated tablet contains Mannitol 44.39 mg (as diluent)
Each film-coated tablet contains Sodium Lauryl Sulfate 0.97 mg

For the full list of excipients, see section 6.1

3. Pharmaceutical form:

Film coated tablet.

Edecil -5 mg: White, Circular biconvex film coated tablets plain on both sides.

Edecil -10 mg: White, Circular biconvex film coated tablets plain on both sides.

Edecil -20 mg: White, Circular biconvex film coated tablets plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications

Edecil tablet is indicated for the management of hypertension (high blood pressure) for end-organ protection.
Prevention of Angina (heart-related chest pain), Prevention of Stroke

4.2 Posology and method of administration

Posology:

Oral route of administration.
The recommended dose for adult is 5mg to 10 mg once daily after breakfast. The dosage can be increased up to Maximum of 20 mg once a day.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients, Left ventricular outflow tract obstruction and untreated congestive cardiac failure.
• Unstable angina pectoris or recent (within 1 month) myocardial infarction, Severe hepatic impairment and Severe renal impairment (GFR < 30 ml/min), including patients undergoing dialysis
•Co-administration with Strong inhibitors of CYP3A4, Ciclosporin, grapefruit or grapefruit juice are also contra-indicated

4.4 Special warnings and precautions for use

• Cilnidipine should be used with caution in patients with hypotension (low blood pressure), heart failure and poor cardiac reserve.
• Cilnidipine should be discontinued in patients who feel chest pain following the administration of the drug.
• Sudden withdrawal of the drug to be avoided as this may exacerbate angina. Therefore, if the discontinuation of Cilnidipine Tablets is necessary, the dosage should be gradually decreased under close observation. If Cilnidipine Tablets is withdrawn from a daily dose of 5 mg, appropriate measures, such as replacement with other antihypertensive agents, should be taken.
Direct the patient not to discontinue this drug without physician's instructions.
• Cilnidipine is not recommended for use in pregnancy and during breastfeeding,
• Cilnidipine should be used with caution if you have liver problems i.e. an impaired liver can lead to the accumulation of this medicine and cause serious side effects
• Cilnidipine should be used with caution in severe kidney problems
•Cilnidipine 10mg tablet is not recommended for use in children below 18 years
•Antiepileptic drugs such as phenytoin and carbamazepine and other drugs include rifampin, quinidine and aldesleukin should also be used with caution along with Cilnidipine.

4.5 Interaction with other medicinal products and other forms of interaction

Cilnidipine Tablets is chiefly metabolized by the drug-metabolizing enzyme CYP3A4 and in part by CYP2C19. Cilnidipine interacts with the following drugs:

• Antipsychotic drugs combined with cilnidipine may result in low blood pressure

• Anti-diabetes medications along with this drug may result in changes in glucose levels, therefore monitoring of glucose levels may be required

• Antiepileptic drugs such as phenytoin and carbamazepine and other drugs include rifampin, Primaquine, Cimetidine, erythromycin, quinidine and aldesleukin

• Consumption of grapefruit juice while taking Cilnidipine can increase the absorption of this medicine in your body

• Caution is advised when consuming alcohol with Cilnidipine

• The blood levels of Amlodipine and Cilnidipine are possibly raised by concurrent use.

Precautions for Coadministration (Cilnidipine Tablets and the following drugs should be administered with care.)

Names of Drugs	**Signs, Symptoms and Treatment**	**Mechanism and Risk Factors**
Agents with hypotensive effect	There is a possibility that blood pressure is excessively decreased.	Drug action is considered to be enhanced additively or synergistically.
Digoxin	It has been reported that some other calcium antagonists (e.g., nifedipine) increased the plasma concentration of digoxin. If any toxic signs/symptoms attributable to digoxin (e.g., nausea, vomiting, headache, abnormal vision, arrhythmia) are observed, appropriate measures should be instituted such as digoxin dose adjustment or discontinuation of Cilnidipine Tablets, depending on the patient's condition	The mechanism is not completely clarified yet, but is thought to lie in decreased renal and extrarenal clearances.
Cimetidine	It has been reported that effects of some other calcium antagonists (e.g., nifedipine) were enhanced.	It is thought that cimetidine decreases hepatic blood flow with the consequent suppression of the enzymatic metabolism of calcium antagonists in liver microsomes, and at

		the same time cimetidine lowers gastric acid output and thus increases absorption of calcium antagonists.
Rifampicin	It has been reported that effects of other calcium antagonists (e.g., nifedipine) were reduced.	It is generally thought that hepatic drug-metabolizing enzyme (cytochrome P-450) induced by rifampicin facilitates metabolism of calcium antagonists and thus increases the clearance of these agents.
Antifungal azoles: Itraconazole, miconazole	The blood concentration of Cilnidipine Tablets may be elevated.	Antimycotic azoles are thought to inhibit CYP3A4, a drug metabolizing enzyme for Cilnidipine Tablets.
Grapefruit juice	It has been demonstrated that the plasma concentration of Cilnidipine Tablets is elevated.	Details of the underlying mechanism remain to be elucidated, but some constituents in grapefruit juice may inhibit CYP3A4, a drug metabolizing enzyme for Cilnidipine Tablets.

4.6 Pregnancy and lactation and Fertility

Fertility

Cilnidipine Tablets should not be administered to women having possibilities of being pregnant. [It has been reported that Cilnidipine Tablets prolongs the gestation period and delivery time in animal experiments (in rats).]

Pregnancy

There are no human clinical or animal data concerning the safety of cilnidipine during pregnancy. Until data are available, administration of Cilnidipine is not recommended for use in pregnancy.

Breastfeeding

Cilnidipine is not recommended for use while breastfeeding. If you are breastfeeding, consult your doctor before taking this medicine.

4.7 Effects on ability to drive and use machines.

It is advised to avoid driving/ and operating machines during the medication of Cilnidipine due to the symptoms such as dizziness that may result from the hypotensive action of the drug.

4.8 Undesirable effects

Clinically significant adverse reactions

1) Hepatic dysfunction and jaundice (frequency unknown):

Hepatic function disorder and jaundice accompanied with increased AST (GOT), ALT (GPT) and γ-GTP may occur. Therefore, close observation should be made, and if any abnormality is observed, appropriate measures, such as discontinuation of Cilnidipine Tablets, should be taken.

2) Thrombocytopenia (incidence: <0.1%): Since thrombocytopenia may occur, close observation should be made, and if any abnormality is observed, appropriate measures, such as discontinuation of Cilnidipine Tablets, should be taken.

If any of the following adverse reactions occur, appropriate measures should be taken depending on the symptoms.

SYSTEM / ORGAN	**0.1 to 5%** **Incidence**	**<0.1% Incidence**	**Incidence unknown**
Hepatic **Note 1**	Increases in AST (GOT), ALT (GPT), LDH, etc.	ALP increased	
Renal	Increases in creatinine or urea nitrogen, urinary protein positive	Urinary sediment present	
Psychoneurological	Headache, headache dull, dizziness, dizziness on standing up, shoulder muscle stiffness	Sleepiness, insomnia, tremor finger, forgetfulness	Numbness
Gastrointestinal	Nausea, vomiting, abdominal pain	Constipation, bloating, thirst, gingival hypertrophy, heartburn, diarrhea	
Cardiovascular	Flushed face, palpitation, feeling hot, electrocardiogram abnormal (ST depressed, inverted T waves), blood pressure decreased	Chest pain, cardiothoracic ratio increased, tachycardia, atrioventricular block, feeling cold	Extrasystole, bradycardia
Hypersensitivity **Note 2**	Rash	Redness, Itching	Photosensitivity
Hematologic	Up or down in WBC, neutrophils and hemoglobin	Up or down in RBC, haematocrit, eosinophils and lymphocytes	
Other	Oedema (facial, lower leg, etc.), general malaise,	Feelings of weakness, gastrocnemius	Tinnitus

	pollakiuria, increased serum cholesterol, up or down in CK (CPK), uric acid, serum K and serum P	muscle cramps, periophthalmic dryness, ocular hyperemia and feeling of irritation, dysgeusia, urine sugar positive, up or down in fasting blood sugar, total protein, serum Ca and CRP, Cough.	

Note 1): The patient should be carefully monitored for these symptoms, and if any abnormality is noted, Cilnidipine Tablets should be discontinued. Note 2): If any such symptom appears, Cilnidipine Tablets should be discontinued. Inform your doctor of undesirable effects occurred during the use of drug.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions ND PQMPs to https://pv.pharmacyboardkenya.org

4.9 Overdose

Overdosage of Cilnidipine Tablets may cause excessive reduction in blood pressure. If reduction in blood pressure is remarkable, appropriate measures such as lifting lower extremities, fluid therapy and administration of vasopressors should be taken. Hemodialytic removal of the drug is not effective because of its high rate of protein binding.

5. Pharmacological properties

5.1 Pharmacodynamics properties

Selective calcium channel blockers with mainly vascular effects – Dihydropyridine derivatives.
ATC code: C08CA14

Cilnidipine is a dihydropyridine calcium channel blocker. It inhibits cellular influx of calcium, thus causing vasodilatation. It has greater selectivity for vascular smooth muscle. Cilnidipine is a vascular selective calcium antagonist, which lowers arterial blood pressure by decreasing peripheral vascular residence.

Antihypertensive Effect:
In various hypertensive animal models (spontaneously hypertensive rats, renal hypertensive rats and dogs, DOCA salt hypertensive rats, and stroke-prone spontaneously hypertensive rats), a single oral dose of cilnidipine showed a gradual and long-lasting hypotensive action that was dose-dependent at 1mg/kg or more. In contrast, it showed a weak hypotensive action in normotensive rats. The duration of the action was not prolonged by an excessive dosage.

In renal hypertensive dogs, cilnidipine showed an additive effect when co-administered with a β-blocker or an angiotensin-converting enzyme inhibitor.
In stroke-prone spontaneously hypertensive rats and renally hypertensive dogs, repeated oral doses of cilnidipine had a stable hypotensive action which did not show attenuation. Discontinuation of cilnidipine did not cause a rebound in blood pressure.
In conscious and unrestrained spontaneously hypertensive rats, cilnidipine did not increase the heart rate during hypotension. Cilnidipine did not increase the plasma noradrenaline level during hypotension, nor did it cause a significant decrease, which an adrenergic blocker (guanethidine sulfate) did. Cilnidipine did not cause orthostatic hypotension, although a ganglion blocker (pentolinium) did in a tilt test using rabbits.
In patients with essential hypertension, a single daily dose of cilnidipine showed a hypotensive action that maintained for 24 hours and was still evident early in the next morning. Power spectral analysis of the R-R intervals of 24 hours electrocardiogram revealed that cilnidipine did not increase sympathetic activity or the heart rate as a reflex response to the reduction of blood pressure.

Inhibitory action on Stress induced Pressor Response
In conscious and unrestrained spontaneously hypertensive rats, cilnidipine inhibited the elevation of blood pressure and plasma norepinephrine levels induced by cold stress. Cilnidipine also inhibited the elevation of blood pressure induced by air jet stress (mental stress) in rats. In healthy adult male volunteers whose blood pressure was elevated by 20% or more in cold stress test, cilnidipine suppressed the elevation of blood pressure induced by cold stress.

Inhibitory action on Sympathetic Stimulation induced Pressor Response
In pithed spontaneously hypertensive rats, cilnidipine suppressed the elevation of blood pressure induced by electrical sympathetic stimulation.
In isolated and perfused mesenteric arterial vascular preparation in spontaneously hypertensive rats, cilnidipine also inhibited the release of norepinephrine induced by electrical sympathetic stimulation.

Effect on Cerebral Circulation
In spontaneously hypertensive rats, cilnidipine did not decrease cerebral blood flow even if the dose which decrease blood pressure by 30-40% in rats was administered. The autoregulation of cerebral blood flow was satisfactorily maintained while the blood pressure was decreased.
In hypertensive patients complicated by cerebrovascular disease, the cerebral blood flow was maintained while blood pressure was lowered.

Effects on Cardiac Function
In dogs, cilnidipine decreased heart rate and myocardial contractility at a higher dose than that inducing an increased flow of arterial blood.
In anesthetized open chest dogs, cilnidipine decreased the myocardial oxygen consumption at dose inducing hypotension. At the time, it neither caused tachycardia nor affected cardiac contractility. In patients with essential hypertension, cilnidipine did not affect heart rate while the blood pressure was decreased and in patients with abnormal cardiothoracic ratio (CTR), it improved the CTR.

Effects on Renal Function
In anesthetized spontaneously hypertensive rats, cilnidipine increased the urinary volume, renal blood flow and glomerular filtration rate at the dose inducing hypotension. Cilnidipine also increased the urinary volume, renal blood flow and glomerular filtration rate, when the renal function was depressed by endothelin.
In patients with essential hypertension, cilnidipine did not affect renal function while the blood pressure was decreased.

Effect on Cardiovascular Disturbance Associated with Hypertension
In stroke-prone spontaneously hypertensive rats, a single daily dose of cilnidipine suppressed the appearance of stroke and improved the survival rate. In addition, it lessened cardiac hypertrophy (increased heart weight), thickening of the ventricular wall, myocardial fibrosis and lesions in the kidney. Moreover, it depressed medial thickening in the coronary arterial wall and decreased calcium content in the aorta.
In patients with essential hypertension, cilnidipine decreased the atherosclerotic index and serum lipid peroxide.

5.2 Pharmacokinetic properties

Absorption and distribution*:* Cilnidipine is completely absorbed from the gastrointestinal tract after administration of Cilnidipine extended-release tablets. The systemic availability of Cilnidipine is approximately 15% in man and is independent of dose in the therapeutic dose range. The plasma protein binding of Cilnidipine is approximately 99.3%. It is bound predominantly to the albumin fraction.

Elimination and metabolism: The average half-life of Cilnidipine in the terminal phase is 1.8-2.2 hours. There is no significant accumulation during long-term treatment. Cilnidipine is extensively metabolized by the liver and all identified metabolites are inactive. Elderly patients and patients with reduced liver function have an average higher plasma concentration of Cilnidipine than younger patients. About 70% of a given dose is excreted as metabolites in the urine; the remaining fraction is excreted in the faeces. Less than 0.5% of a dose is recovered unchanged in the urine. The kinetics of Cilnidipine is not changed in patients with renal impairment.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose pH 102
Mannitol
Polyvinyl pyrrolidone
Purified water
Sodium Lauryl sulphate
Aerosil
Crospovidone
Magnesium stearate
Tabcoat TC 58118 white

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30^{o}C. Protect from light.

6.5 Nature and contents of container

Pack style: 3 x 10 Tablets
10 Tablets are packed in Alu-Alu blister.
Such 3 blisters are enclosed in one carton with a package insert.

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. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
Dawa Limited,
Plot No. 7879/8, Baba Dogo Road, Ruaraka,
P.O Box 16633-00620,
Nairobi, Kenya.

Manufacturing site address:
Dawa Limited,
Plot No. 7879/8, Baba Dogo Road, Ruaraka,
P.O Box 16633-00620,
Nairobi, Kenya.

8. Marketing authorization number

Edecil 5 mg Tablet: CTD10549
Edecil 10 mg Tablet: CTD10551
Edecil 20 mg Tablet: CTD10550

9. Date of first registration

Edecil 5 mg Tablet: 03/08/2023
Edecil 10 mg Tablet: 03/08/2023
Edecil 20 mg Tablet: 03/08/2023

10. Date of revision of the text:

15/09/2023

11. Dosimetry:

Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:

Not Applicable