SUMMARY OF PRODUCT CHARACTERISTICS

1.	**Name of the Medical Product**
	1.1 Product Name : CINOD 5 (Cilnidipine Tablets 5 mg) **CINOD 10 (**Cilnidipine Tablets 10 mg)
	1.2 Strength : **CINOD 5 (**Cilnidipine Tablets 5 mg**)** Each film coated tablet contains: Cilnidipine 5 mg **CINOD 10 (**Cilnidipine Tablets 10 mg**)** Each film coated tablet contains: Cilnidipine 10 mg
	1.3 Pharmaceutical Dosage Form : Tablet
2.	**Qualitative & Quantitative Composition:** **CINOD 5** (Cilnidipine Tablets 5 mg) Each film coated tablet contains: Cilnidipine 5 mg Colour: Titanium Dioxide **CINOD 10** (Cilnidipine Tablets 10 mg) Each film coated tablet contains: Cilnidipine 10 mg Colour: Lake of Sunset Yellow FCF and Titanium Dioxide. For a full list of excipients, see section 6.1 of SmPC
3.	**Pharmaceutical Form:**
	Tablet **CINOD 5 (**Cilnidipine Tablets 5 mg**)** White to off white coloured, circular, biconvex, film coated tablets, plain on both sides. **CINOD 10** (Cilnidipine Tablets 10 mg**)** Light orange to orange coloured, circular, biconvex, film coated tablets, plain on both sides.
4.	**Clinical Particulars**
	4.1 Therapeutic Indications: Treatment of hypertension.
	4.2 Posology and Method of administration: **Adults**: 5-10 mg once a day after breakfast. The dosage may be adjusted according to the patient's age and symptoms. The dose can be increased up to 20 mg once a day, if a sufficient response does not appear. **Severe Hypertension**: 10-20 mg once a day for oral use after breakfast. **Administration:** For oral use.
	4.3 Contraindications: Hypersensitivity to Cilnidipine or to any of the excipients of Cinod. **Use in pregnancy**: Pregnant women or women having possibilities of being pregnant. Cinod should not be administered to pregnant women or women having possibilities of being

pregnant. It has been reported that Cilnidipine prolongs the gestation period and delivery time in animal experiments (in rats).

4.4 Special warning and precautions for use:

Cilnidipine should be administered with care in the following:

1. Patients with serious hepatic dysfunction (the plasma concentration may become elevated);
2.Patients with a history of serious adverse reactions to calcium antagonists.
3.Cilnidipine contains lactose.

1. As it has been reported that sudden withdrawal of a calcium antagonist caused aggravation of certain symptoms. Therefore, if the discontinuation of Cilnidipine is necessary, the dosage should be gradually decreased under close observation. If Cilnidipine is withdrawn from a daily dose of 5 mg, appropriate measures e.g., replacement with other antihypertensive agents, should be taken.

2. As it may cause dizziness, patients should be advised to be careful while operating machines or while driving.

Use in children: The safety of Cilnidipine in pediatric patients has not been established (no clinical experience).

Use in the elderly: Cilnidipine should be administered carefully under close observation of the patient's condition, taking such measures as starting with a lower dose (e.g., 5 mg). It is generally acknowledged that the excessive hypotensive action should be avoided in the elderly. Therefore, adverse reactions (including abnormalities in laboratory data) in the elderly ≥65 years, were observed in 152 of 2,863 patients in the investigation at the time of approval and the post-marketing studies (at the end of the re-examination period).

4.5 Interactions with other medicinal products and other forms of Interactions :
Cilnidipine is chiefly metabolized by the drug-metabolizing enzyme CYP3A4 and in part by CYP2C19.

<u>Care to be taken with Combination</u>

Drugs having a hypotensive action	Blood pressure is likely to excessively decrease.	It has been considered to enhance the additive or synergistically.
Digoxin	The simultaneous administration of Cilnidipine(like Nifedipine and other CCB)and digoxin may lead to reduced clearance resulting in an increase in plasma concentrations of digoxin. Since there have been isolated reports of patients with elevated digoxin levels, and there is a possible interaction between digoxin and Cilnidipine, it is recommended that digoxin levels be monitored when initiating, adjusting and discontinuing Cilnidipine to avoid possible over- or under- digitalization	Mechanism is not fully understood but is thought to be due to digoxin renal and extra-renal clearance is reduced.

Cimetidine	The action of the other calcium antagonists (nifedipine, etc.) is enhanced have been reported.	Cimetidine lowers the hepatic blood flow, while inhibiting the enzymatic metabolism in liver microsomes of calcium antagonists, reduce gastric acid, it is believed to increase the absorption of calcium antagonists.
Rifampicin	Action of other calcium antagonists (nifedipine, etc.) have been reported to be attenuated.	Hepatic drug metabolizing enzymes induced by rifampicin (cytochrome P450) promotes the metabolism of calcium antagonists are thought to increase the clearance.
Azole antifungal agents itraconazole miconazole, etc.	Blood concentrations of this drug is likely to rise.	Azole antifungal agent is considered to inhibit the CYP3A4 of drug-metabolizing enzymes of this drug.
Grapefruit juice	It has been confirmed that the blood concentration of this drug is increased.	The details expression mechanism of which is unclear, components contained in grapefruit juice is considered to inhibit the CYP3A4 in drug metabolism enzymes of this drug.

4.6 Pregnancy and Lactation:

Use in pregnancy: Pregnant women or women having possibilities of being pregnant. Cinod should not be administered to pregnant women or women having possibilities of being pregnant. It has been reported that Cilnidipine prolongs the gestation period and delivery time in animal experiments (in rats).

Use in lactation: It is advisable to avoid the administration of Cilnidipine to nursing mothers. However, if the administration is indispensable, the patient should be instructed to discontinue lactation. Transfer of Cilnidipine to mother's milk has been reported in animal experiments (in rats).

4.7 Effects on ability to drive and use machine:

The symptoms e.g., dizziness may occur because of the hypotensive action from Cilnidipine. Give warning against engaging in hazardous activities requiring alertness e.g., working at a height, operating machinery or driving motor vehicles.

4.8 Undesirable Effects:

Adverse reactions, including abnormalities in laboratory data, were observed in 414 (6.95%) of 5,958 patients in the investigations at the time of approval and the post marketing studies (at the end of the re-examination period).

Clinically Significant Adverse Reactions:

Hepatic Dysfunction and Jaundice (Frequency Unknown): Hepatic function disorder and jaundice accompanied with increased aspartate aminotransferase (AST) [glutamic oxaloacetic transaminase (GOT)], alanine aminotransferase (ALT) [glutamic pyruvic transaminase (GPT)]

and γ-glutamyl transpeptidase (GTP) may occur. Therefore, close observation should be made, and if any abnormality is observed, appropriate measures e.g., discontinuation of Cilnidipine, should be taken.

Thrombocytopenia (Incidence: <0.1%): Since thrombocytopenia may occur, close observation should be made and if any abnormality is observed, appropriate measures e.g., discontinuation of Cilnidipine, should be taken.

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

	Frequency unknown
Liver	AST (GOT), ALT (GPT), LDH, elevated, such as Al-P
kidney	Rise of creatinine urea nitrogen, urinary protein positive, urinary sediment positive
Neuropsychiatric	Headache, heaviness of the head, dizziness, lightheadedness, stiff neck, drowsiness, insomnia, hand tremors, forget things, numbness
Circulatory organ	Hot flushes, palpitations, hot flashes, abnormal electrocardiogram (ST decrease, T-wave inversion), decreased blood pressure, chest pain, increased cardiothoracic ratio, tachycardia, atrioventricular block, cold sensation, premature contraction, bradycardia
Digestive organ	Nausea, vomiting, abdominal pain, constipation, abdominal distension, dry mouth, gingival hyperplasia, heartburn, diarrhea
Hypersensitivity	Rash, redness, itching, photosensitivity disease
blood	The number of white blood cells, neutrophils, hemoglobin, red blood cell count, hematocrit, eosinophils, fluctuation of lymphocyte
Other	Edema (face, lower limbs, etc.), general malaise, frequent urination, elevate serum cholesterol, CK (CPK) · uric acid-variation of serum K · serum P, weakness, musculus gastrocnemius spasticity, dry around the eyes, the eyes of hyperemia irritation, abnormal taste, urine sugar positive, change of fasting blood glucose, total protein, serum Ca · CRP, cough, tinnitus

4.9 Overdosage:

Over dosage of Cilnidipine may cause excessive reduction in blood pressure. If reduction in blood pressure is remarkable, appropriate measures e.g., lifting lower extremities, fluid therapy and administration of vasopressors should be taken.

Hemodialytical removal of Cilnidipine is not effective because of its high rate of protein-binding.

5. Pharmacological properties

5.1 Pharmacodynamic Properties:

Pharmacodynamics

Mechanism of Action:

Experimental data suggest that Cilnidipine binds to the dihydropyridine binding sites of the L-type voltage dependent calcium channel and inhibits Ca2+ influx across the cell membranes of vascular smooth muscle cells via this channel (rabbits in vitro). Consequently, vascular smooth

	muscle is relaxed, causing vasodilation. Through this mechanism, Cilnidipine is considered to have a hypotensive action. Cilnidipine inhibits Ca2+ influx via N-type voltage dependent calcium channels in the sympathetic nerve cell membrane. The inhibition of Ca2+ influx via N-type voltage dependent calcium channel was observed over a similar range of drug concentrations to those inhibiting L-type voltage dependent Ca2+ channels (rats in vitro). Consequently, release of norepinephrine from sympathetic nerve terminals would be inhibited. Cilnidipine is considered to suppress the reflex increase in heart rate which may be mediated by sympathetic activation after blood pressure reduction and to inhibit stress-related hypertension through this mechanism
	5.2 Pharmacokinetics Properties: **Plasma Drug Levels**: When a single dose of Cilnidipine 5-, 10- or 20 mg was orally administered to 6 healthy male volunteers, the peak plasma concentration (Cmax) was found to be 4.7 ng/mL, 5.4 ng/mL and 15.7 ng/mL, respectively and the area under the concentration-time curve (AUC0-24) to be 23.7 ng·hr/mL, 27.5 ng·hr/mL and 60.1 ng·hr/mL, respectively. Thus, both parameters increased in a dose dependent manner. When a single dose of Cilnidipine 10 mg was repeatedly administered once a day to 6 healthy male volunteers, pharmacokinetic parameters of Cilnidipine were indicated as follows. The plasma concentration reached a steady-state from Day 4 of the administration and there was no evidence of the accumulation. The pharmacokinetics of Cilnidipine have also been evaluated in patients with impaired renal function (serum creatinine: 1.5-3.1 mg/dL) following a single oral dose of 10 mg in the hypertensive patients and no significant differences were found in the pharmacokinetic profile of Cilnidipine compared with that in patients with normal renal function. Repeated oral administration of Cilnidipine at a dose of 10 mg once a day for 7 days in patients with impaired renal function caused no differences in the pharmacokinetic profile compared with that in patients with normal renal function. **Metabolism and Excretion**: From the metabolites identified in the plasma and urine of healthy male volunteers, it is considered that the major route of Cilnidipine metabolism is demethylation of the methoxyethyl group followed by hydrolysis of the cinnamyl ester and oxidation of the dihydropyridine ring. It is considered that CYP3A4 is mainly involved and CYP2C19 is partly involved in the demethylation of the methoxyethyl group (in vitro). The calcium channel blocking action of the metabolite with the demethylated methoxyethyl group was only 1/100 of that of the parent compound (in rabbits). When a single oral dose of Cilnidipine 10 mg was repeatedly administrated to healthy male volunteers once a day for 7 days, no unchanged compound of Cilnidipine but 5.2% of the dose was excreted in the urine as metabolites. (The approved administration of Cilnidipine is orally once a day after breakfast.) An in vitro experiment showed that Cilnidipine was 99.3% bound to human serum protein.
	5.3 Preclinical Safety data: There is no information on Cilnidipine. However, high doses of other calcium channel blockers have been tolerated in rats and dogs without toxic effects. Preclinical data, in other calcium channel blockers, based on studies in the rat and rabbit, reveal no special hazards for humans for teratogenicity or embryotoxicity.
6.	**Pharmaceutical particulars**
	6.1 List of Excipients: **CINOD 5 (Cilnidipine Tablets 5mg)** Microcrystalline Cellulose, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Instacoat SOL IC-S-223 White, Isopropyl Alcohol and Dichloromethane (Methylene Chloride).

	CINOD 10 (Cilnidipine Tablets 10mg) Microcrystalline Cellulose , Croscarmellose Sodium, Colour Sunset Yellow Lake , Colloidal Silicon Dioxide , Magnesium Stearate , Instacoat SOL IC-S-3104 Orange , Isopropyl Alcohol and Dicloromethane (Methylene Chloride).
	6.2 Incompatibilities: Not applicable
	6.3 Shelf life: 24 months
	6.4 Special Precautions for storage: Store below 30°C.
	6.5 Nature and contents of container: 10 tablets in Alu-Alu blister pack, 3 such blisters in a printed carton along with Patient Information Leaflet.
	6.6 Special precautions for disposal: Not applicable
	6.7: Category of Distribution: Prescription Only Medicine (POM)
7.	**Marketing Authorization Holder:** Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (West), Mumbai- 400 067, India **Manufacturing Site Address:** Ajanta Pharma Limited Palashbari, Mirza, Mirza, Palashbari Road, Kamrup (Rural), Assam
8.	**Marketing Authorization Numbers:** Not applicable
9.	**Date of first registration /renewal of the registration:** Not Applicable
10.	**Date of revision of text:** Dec 27, 2021