Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Cachmont-LC Tablets

2. Qualitative and quantitative composition
Cachmont-LC Tablets Each uncoated tablet contains:
Montelukast Sodium BP
Equivalent to Montelukast 10mg
Levocetirizine Dihydrochloride USP 5mg

Excipients with known effect: Mannitol

3. Pharmaceutical form
Pale yellow coloured round shaped biconvex un-coated tablet plain on both side.

4. Clinical particulars

4.1 Therapeutic indications
Cachmont-LC TABLETS are indicated for relief of symptoms of allergic rhinitis (seasonal and perennial) and Management of comorbid asthma and allergic rhinitis.

4.2 Posology and method of administration
Posology
Adults (>15 years): 1 tablet once daily

Method of administration
For oral use

4.3 Contraindications
It is contraindicated in patients with known hypersensitivity to Montelukast Sodium, Levocetirizine or Cetirizine or to any other component of this product. It is also contraindicated in patients with severe renal impairment at less than 10mL/min creatinine clearance.

4.4 Special warnings and precautions for use

BLACKBOX WARNING

Serious Neuropsychiatric Events

·Serious neuropsychiatric events have been reported in patients taking MONTELUKAST

· Discuss benefits and risks of MONTELUKAST with patients and caregivers

· **Monitor for neuropsychiatric symptoms in patients taking MONTELUKAST**

· **Discontinue MONTELUKAST immediately if neuropsychiatric symptoms occur**

· **Because the benefits of MONTELUKAST may not outweigh the potential risk of neuropsychiatric symptoms in patients with allergic rhinitis, reserve use for patients who have an inadequate response or intolerance to alternative therapies**

Monteukast:
Montelukast is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. Patients should be advised to have appropriate rescue medication available. Therapy with Montelukast can be continued during acute exacerbations of asthma. While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, Montelukast should not be abruptly substituted for inhaled or oral corticosteroids. Montelukast should not be used as monotherapy for the treatment and management of exercise-induced bronchospasm. Patients who have exacerbations of asthma after exercise should continue to use their usual regimen of inhaled (beta)-agonist as prophylaxis and have available for rescue a short-acting inhaled (beta)-agonist. Patients with known aspirin sensitivity should continue avoidance of aspirin or nonsteroidal antiinflammatory agents while taking Montelukast. Eosinophilic Conditions: In rare cases, patients on therapy with Montelukast may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. Montelukast sodium Levocetirizine dihydrochloride These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Levocetirizine dihydrochloride: Precaution is recommended with intake of alcohol. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Renal Impairment: As Levocetirizine is mainly excreted through urine, dosage adjustment may be required in patients with impaired renal function. Hence this combination should be used with caution in such patients. Hepatic Impairment: As Montelukast is mainly excreted through bile, caution is to be exercised while prescribing this combination in patients with impaired hepatic function. Use in Children: The safety and effectiveness of Montelukast and Levocetirizine at 10 mg and 5 mg respectively in pediatric patients under 15 years of age have not been established. Use in Elderly: Montelukast: No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Levocetirizine dihydrochloride:

Clinical studies of Levocetirizine for each approved indication did not include sufficient number of patients aged 65 years and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy**.**

4.5 Interaction with other medicinal products and other forms of interaction

Montelukast in drug-interaction studies, the recommended clinical dose of Montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, prednisolone, oral contraceptives (norethindrone 1 mg/ethinyl estradiol 35 mcg), terfenadine, digoxin, and warfarin. Although additional specific interaction studies were not performed, Montelukast was used concomitantly with a wide range of commonly prescribed drugs in clinical studies without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants. Phenobarbital, which induces hepatic metabolism, decreased the AUC of Montelukast approximately 40% following a single 10mg dose of Montelukast. No dosage adjustment for Montelukast is recommended. It is reasonable to employ appropriate clinical monitoring when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are co-administered with Montelukast. Levocetirizine dihydrochloride: In vitro data indicate that Levocetirizine is unlikely to produce pharmacokinetic interactions through inhibition or induction of liver drug metabolizing enzymes. No in vivo drug-drug interaction studies have been performed with Levocetirizine. Drug interaction studies have been performed with racemic cetirizine. Pharmacokinetic interaction studies performed with racemic cetirizine demonstrated that cetirizine did not interact with antipyrine, pseudoephedrine, erythromycin, azithromycin, ketoconazole and cimetidine. There was a small decrease (~16%) in the clearance of cetirizine caused by a 400 mg dose of theophylline. It is possible that higher theophylline doses could have a greater effect. Ritonavir increased the plasma AUC of cetirizine by about 42% accompanied by an increase in half-life (53%) and a decrease in clearance (29%) of cetirizine. The disposition of ritonavir was not altered by concomitant cetirizine administration.

4.6 Pregnancy and Lactation

Pregnancy: There are no adequate and well-controlled studies of either Montelukast or Levocetirizine in pregnant women. Hence this combination should not be used during pregnancy.

Lactation: Since Levocetirizine is excreted in breast-milk the combination is not recommended during lactation.

4.7 Effects on ability to drive and use machines

Comparative clinical trials have revealed no evidence that levocetirizine at the recommended dose impairs mental alertness, reactivity or the ability to drive. In clinical trials the occurrence of somnolence, fatigue, and asthenia has been reported in some patients under therapy with levocetirizine. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, and motor coordination such as operating machinery or driving a motor vehicle after ingestion of levocetirizine. Concurrent use of levocetirizine with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur.

4.8 Undesirable effects

There is no data available on undesirable effects of this combination. However, side effects have been reported with individual molecules.

Montelukast: Common side effects include dyspepsia, abdominal pain, rash, dizziness, headache, fatigue, fever, trauma, cough, nasal congestion, infuenza. The following adverse reactions have been reported in post-marketing use: Blood and lymphatic system disorders: increased bleeding tendency.

Hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration.

Psychiatric disorders: Dream abnormalities including nightmares, hallucinations, insomnia, irritability, anxiety, restlessness, agitation including aggressive behaviour, tremor, depression, suicidal thinking and behaviour (suicidality) in very rare cases.

Nervous system disorders:Dizziness, drowsiness, paraesthesia/hypoesthesia, seizure.

Respiratory, thoracic and mediastinal disorders: Epistaxis. Cardiac disorders: Palpitations.

Gastrointestinal disorders: Diarrhea, dry mouth, dyspepsia, nausea, vomiting.

Hepatobiliary disorders: Elevated levels of serum transaminases (ALT, AST), rare cases of cholestatic hepatitis, hepatocellular liver-injury, and mixed-pattern liver injury have been reported in patients treated with Montelukast. Most of these occurred in combination with other confounding factors, such as use of other medications, or when montelukast was administered to patients who had underlying potential for liver disease, such as alcohol use or other forms of hepatitis.

Skin and subcutaneous tissue disorders: Angioedema, bruising, urticaria, pruritus, rash, erythema nodosum.
Musculoskeletal and connective tissue disorders: arthralgia, myalgia including muscle cramps.

General disorders and administration site conditions: Asthenia/fatigue, malaise, edema. Very rare cases of Churg-Strauss Syndrome (CSS) have been reported during montelukast treatment in asthmatic patients. In rare cases, patients with asthma on therapy with Montelukast may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome. A causal association between Montelukast and these underlying conditions has not been established.

Levocetirizine dihydrochloride: Use of Levocetirizine has been associated with somnolence, fatigue, nasopharyngitis, dry mouth, and pharyngitis in subjects 12 years of age and older. Further uncommon incidences of adverse reactions like asthenia or abdominal pain were observed. In addition to the adverse reactions reported during clinical studies and listed above, very rare cases of the following adverse drug reactions have been reported in post-marketing experience.

Immune system disorders: Hypersensitivity including anaphylaxis.

Psychiatric disorders: Aggression, agitation.

Nervous system disorders: Convulsion.

Eye disorders: Visual disturbances.

Cardiac disorders: Palpitations.

Respiratory, thoracic, and mediastinal disorders: Dyspnea.

Gastrointestinal disorders: Nausea.

Hepatobiliary disorders: Hepatitis.

Skin and subcutaneous tissue disorders: Angioneurotic edema, fixed drug eruption, pruritus, rash, urticaria Musculoskeletal, connective tissues.

Bone disorders: Myalgia.

Investigations: Weight increased, abnormal liver function tests.

Reporting of Adverse Drug Reactions
Healthcare professionals are asked to report any suspected adverse drug reactions via the Pharmacy and Poisons Board's; Pharmacovigilance-

Electronic-Reporting-System(PvERS)
https://pv.pharmacyboardkenya.org/

4.9 Overdose

There is no data reported on the overdosage of this combination. However, overdosage has been reported with individual molecules. Montelukast: There have been reports of acute overdosage in post-marketing experience and clinical studies with Montelukast. These include reports in adults and children with a dose as high as 1000 mg. The clinical and laboratory findings observed were consistent with the safety profile in adults and pediatric patients. There were no adverse experiences in the majority of overdosage reports. The most frequently occurring adverse experiences were consistent with the safety profile of Montelukast and included abdominal pain, somnolence, thirst, headache, vomiting and psychomotor hyperactivity. It is not known whether Montelukast is removed by peritoneal dialysis or hemodialysis. Levocetirizine dihydrochloride: Symptoms of overdose may include drowsiness in adults, and in children, initially agitation and restlessness, followed by drowsiness. There is no known specific antidote to levocetirizine. Should overdose occur, consider standard measures to remove any unabsorbed drug. Gastric lavage should be considered following short-term ingestion. Levocetirizine is not effectively removed by hemodialysis. Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Montelukast:

The cysteinyl leukotrienes (LTC4, LTD4, LTE4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 (CysLT1) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction. Montelukast is an orally active compound that binds with high affinity and selectivity to the CysLT1 receptor. Montelukast inhibits physiologic action of LTD4 at the CysLT1 receptor without any agonist activity.

Levocetirizine dihydrochloride:

Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H1-receptors. Binding studies revealed that levocetirizine has high affinity for human H1-receptors (Ki=3.2 nmol/l). Levocetirizine has an affinity 2-fold higher than that of cetirizine (Ki=6.3 nmol/l). Levocetirizine dissociates from H1-receptors with a half-life of 115 ± 38 min. After single administration, levocetirizine shows receptor occupancy of 90% at 4 hours and 57% at 24 hours. The onset of action of levocetirizine 5 mg in controlling pollen-induced symptoms has been observed at 1 hour post drug intake in placebo-controlled trials in the model of the allergen challenge chamber. In vitro studies (Boyden chambers and cell layers techniques) show that levocetirizine inhibits eotaxin-induced eosinophil transendothelial migration through both dermal and lung cells. A pharmacodynamic experimental study in vivo (skin chamber technique) showed three main inhibitory effects of levocetirizine 5 mg in the first 6 hours of pollen-induced reaction, compared with placebo in 14 adult patients: Inhibition of VCAM-1 release, modulation of vascular permeability, and a decrease in eosinophil recruitment. Pharmacodynamic studies in healthy volunteers demonstrate that, at half the dose, levocetirizine has comparable activity to cetirizine, both in the skin and in the nose. Pharmacokinetic/pharmacodynamic relationship 5 mg Levocetirizine provide a similar pattern of inhibition of histamine-induced wheal and flare than 10 mg cetirizine. As for cetirizine, the action on histamine-induced skin reactions was out of phase with the plasma concentrations. ECGs did not show relevant effects of levocetirizine on QT interval.

5.2 Pharmacokinetic properties

Montelukast

Absorption: After administration of the 10-mg to fasted adults, the mean peak montelukast plasma concentration (Cmax) is achieved in 3 to 4 hours (Tmax). The mean oral bioavailability is 64%. The oral bioavailability and Cmax are not influenced by a standard meal in the morning. The safety and efficacy of Montelukast in patients with asthma were demonstrated in clinical trials in which the 10-mg film-coated tablets were administered in the evening without regard to the time of food ingestion. The safety and efficacy of montelukast in patients with seasonal allergic rhinitis were demonstrated in clinical trials in which the 10-mg film-coated tablet was administered in the morning or evening without regard to the time of food ingestion.

Distribution: Montelukast is more than 99% bound to plasma proteins. The steady state volume of distribution of montelukast averages 8 to 11 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours post dose were minimal in all other tissues.

Metabolism: Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast

are undetectable at steady state in adults and pediatric patients. In vitro studies using human liver microsomes indicate that cytochromes P450 3A4 and 2C9 are involved in the metabolism of montelukast. Clinical studies investigating the effect of known inhibitors of cytochromes P450 3A4 (e.g., ketoconazole, erythromycin) or 2C9 (e.g., fluconazole) on montelukast pharmacokinetics have not been conducted. Based on further in vitro results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. However, in vitro studies have shown that montelukast is a potent inhibitor of cytochrome P450 2C8; however, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of drugs primarily metabolized by CYP2C8) demonstrated that montelukast does not inhibit CYP2C8 in vivo, and therefore is not anticipated to alter the metabolism of drugs metabolized by this enzyme.

Elimination: The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and < 0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile. In several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast is nearly linear for oral doses up to 50 mg. During once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (14%). In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction. Montelukast is an orally active compound that binds with high affinity and selectivity to the CysLT1 receptor. Montelukast inhibits physiologic action of LTD4 at the CysLT1 receptor without any agonist activity.

Levocetirizine dihydrochloride:

The pharmacokinetics of levocetirizine is linear with dose and time independent with low inter-subject variability. The pharmacokinetic profile is the same when given as the process of absorption and elimination.

Absorption: Levocetirizine is rapidly and extensively absorbed following oral administration. Peak plasma concentrations are achieved 0.9 h after dosing. Steady state is achieved after two days. Peak concentrations are typically 270 ng/ml and 308 ng/ml following a single and a repeated 5 mg o.d. dose, respectively. The extent of absorption is dose-independent and is not altered by food, but the peak concentration is reduced and delayed. Distribution: No tissue distribution data are available in humans, neither concerning the passage of levocetirizine through the

blood-brain-barrier. Levocetirizine is 90% bound to plasma proteins. The distribution of levocetirizine is restrictive, as the volume of distribution is 0.4 l/kg.

Biotransformation: The extent of metabolism of levocetirizine in humans is less than 14% of the dose and therefore differences resulting from genetic polymorphism or concomitant intake of enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, Nand O-dealkylation and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4 while aromatic oxidation involved multiple and/or unidentified CYP isoforms. Levocetirizine had no effect on the activities of CYP isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 at concentrations well above peak concentrations achieved following a 5 mg oral dose. Due to its low metabolism and absence of metabolic inhibition potential, the interaction of levocetirizine with other substances, or vice-versa, is unlikely.

Elimination: The plasma half-life in adults is 7.9 ± 1.9 hours. The mean apparent total body clearance is 0.63 ml/min/kg. The major route of excretion of levocetirizine and metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via feces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

5.3 Preclinical safety data

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

6. Pharmaceutical Particulars

6.1 List of Excipients

Hydroxy Propyl Cellulose LF (Klucel LF)
Mannitol
Avicel (PH 101)
Avicel (PH 101)
Mannitol (Praritop) 200 SD
Magnesium Stearate
Veegum-R
Crosscarmellose Sodium

6.2 Incompatibilities

N/A

6.3 Shelf-Life

2 years

6.4 Special Precautions for storage

Store in a dry place below 30°C. Protect from light. Keep out of reach of children.

6.5 Nature and Content of container
Carton Containing 10 X 10 Alu-Alu Blisters along 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
Cachet Pharmaceuticals Pvt. Ltd
415, Shah Nahar Industrial Estate,
Dr. E. Moses Road, Worli, Mumbai-400 018,
Maharashtra, India**.**

8. Marketing Authorization Number
CTD10461

9. Date of first authorization/renewal of the authorization
08/11/2023

10. Date of revision of the text
13/05/2024