SUMMARY PRODUCT CHARACTERISTICS (SPC)

1. Name of the Medicinal Product:

Product Name: MONTECOR PLUS KID (Montelukast and Levocetirizine Hydrochloride Dispersible Tablets)

2. Qualitative and Quantitative Composition

Each uncoated dispersible tablet contains
Montelukast Sodium USP

Eq. to Montelukast….4 mg

Levocetirizine Hydrochloride …. 2.5 mg

For full list of excipients see section 6.1

3. Pharmaceutical Form: Uncoated Dispersible Tablets

4. Clinical Particulars

4.1 Therapeutic indications:

MONTECOR PLUS KID tablets are indicated for the relief of symptoms of allergic rhinitis [seasonal or perennial], as prophylaxis in seasonal allergic rhinitis and treatment of comorbid asthma and allergic rhinitis in patients 2 to 5 years of age.

4.2 Posology and Method of administration:

For oral use. As directed by physician.

4.3 Contraindications

MONTECOR PLUS KID is contraindicated in patients with known hypersensitivity to montelukast sodium, levocetirizine or cetirizine or to any other component of this product.

4.4 Special warning and precautions for use:

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.

These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy.

Levocetirizine

Patients should avoid engaging in hazardous occupation requiring complete mental alertness such as driving or operating machinery when taking levocetirizine. Precaution is recommended with intake of alcohol and in those who are on CNS depressants.

4.5 Interaction with other medicinal products and other forms of Interactions 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 10-mg 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

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.
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.
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.

4.6 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:

Patients should avoid engaging in hazardous occupation requiring complete mental alertness such as driving or operating machinery when taking levocetirizine.

4.8 Side effects:

Montelukast & Levocetirizine are generally well tolerated. Common side effects which might be seen with the combination are dyspepsia, abdominal pain, rash, dizziness, headache, fatigue, fever, trauma, cough, nasal congestion, and somnolence. In rare cases, patients may present with systemic eosinophilia, sometimes presenting with clinical features of consistent with Churg-Strauss Syndrome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. Healthcare professionals are requested to report any suspected adverse reactions via the Pharmacy and Poisons Reporting System (PvERS) https://pv.pharmacyboardkenya.org"

4.9 OVERDOSAGE

There is no data to prove the overdosage of this combination. However, overdosage has been reported with individual molecules.

Montelukast: There have been reports of acute over-dosage 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 6 consistent with the safety profile in adults and pediatric patients. There were no adverse experiences in most over-dosage 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: Symptoms of overdose may include drowsiness in adults and

initially agitation and restlessness followed by drowsiness, in children. There is no known specific antidote to levocetirizine. Should overdose occur, symptomatic or supportive treatment is recommended. Levocetirizine is not effectively removed by dialysis and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested.

5. Pharmacological Properties:

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: Leukotriene receptor antagonist, Antihistamines for systemic use, piperazine derivative

ATC Code

Montelukast:

R03DC03

Levocetirizine:

R06AE09

Montelukast: Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD4 in asthmatics. Doses as low as 5 mg cause substantial blockage of LTD4 -induced bronchoconstriction.

Levocetirizine: 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.

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 Pharmacokinetic

Properties Montelukast:

***Absorption*:** After administration of a 10-mg film-coated tablet 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.

***Distribution*:** Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 11 liters.

***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.

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 are 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%).

Levocetirizine

The pharmacokinetics of levocetirizine are linear with dose and time-independent with low inter-subject variability. The pharmacokinetic profile is the same when given as the single enantiomer or when given as cetirizine. No chiral inversion occurs during the process of absorption and elimination.

***Absorption*:** Levocetirizine is rapidly and extensively absorbed following oral administration. Peak plasma concentrations are achieved 0.9h 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. 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, N- and O-dealkylation and taurine conjugation. 3 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. 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:

In animal toxicity studies, minor serum biochemical alterations in ALT, glucose, phosphorus and triglycerides were observed which were transient in nature. The signs of toxicity in animals were increased excretion of saliva, gastro-intestinal symptoms, loose stools and ion imbalance. These occurred at dosages which provided>17-fold the systemic exposure seen at the clinical dosage. In monkeys, the adverse effects appeared at doses from 150 mg/kg/day (>232-fold the

systemic exposure seen at the clinical dose). In animal studies, montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure by greater than 24-fold. A slight decrease in pup body weight was noted in the female fertility study in rats at 200 mg/kg/day (>69fold the clinical systemic exposure). In studies in rabbits, a higher incidence of incomplete ossification, compared with concurrent control animals, was seen at systemic exposure>24-fold the clinical systemic exposure seen at the clinical dose. No abnormalities were seen in rats. Montelukast has been shown to cross the placental barrier and is excreted in breast milk of animals.

No deaths occurred following a single oral administration of montelukast sodium at doses up to 5000 mg/kg in mice and rats (15,000 mg/m2 and 30,000 mg/m2 in mice and rats, respectively), the maximum dose tested. This dose is equivalent to 25,000 times the recommended daily adult human dose (based on an adult patient weight of 50 kg).

Montelukast was determined not to be phototoxic in mice for UVA, UVB or visible light spectra at doses up to 500 mg/kg/day (approximately>200-fold based on systemic exposure).

Montelukast was neither mutagenic in in vitro and in vivo tests nor tumorigenic in rodent species. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. Pharmaceutical Particulars:

6.1 List of excipients:

1. Mannitol BP
2. Lactose BP
3. Maize Starch BP
4. Indion-234 IH
5. Colloidal Anhydrous Silica BP
6. Dry Peppermint (Trusil) IH
7. Dry Orange Flavour IH
8. Aspartame BP
9. Purified Talc BP

10. Sodium Bicarbonate BP

6.2 Incompatibilities: Not known

6.3 Shelf life: 24 Months

6.4 Special precautions for storage: None

6.5 Nature and contents of container:

Primary Packing : 10 tablets to be packed in Alu-Alu Blister.

Secondary Packing : Such 1 Blister to be packed in a carton along with pack insert.

6.6 Special Precaution for Disposal and other handling: None

7. Marketing Authorization Holder:

Company name: Signature Healthcare Ltd.

Address : Cape Business Park, Along Thika Super Highway P.O.Box 66172-00800, Nairobi.

Country : KENYA

Mobile : +254-705617118

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E-Mail : info@signaturehealthcareltd.com, mohamediftikharsaeed@gmail.com, info@signaturehealthcareltd.co.ke

8. Marketing Authorization Numbers : --
Kenya : H2022/CTD9681/21280

9. Date of first authorization/renewal of the authorization:

10. Date of revision of the text: --