SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

GULAIR TABLETS

2. Qualitative and quantitative composition

Each Film Coated Tablet Contains:
Levocetirizine Dihydrochloride USP ..... 5 mg
Montelukast Sodium BP ..... 10 mg

Excipient with known effect
Each 5 mL also contains 4 mg of methyl hydroxybenzoate and 1 mg of propyl hydroxybenzoate (see section 4.4).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Montelukast & Levocetirizine Tablet is indicated for relief of symptoms of allergic rhinitis (seasonal and perennial), as prophylaxis in seasonal allergic rhinitis and treatment of comorbid asthma and allergic rhinitis.

4.2 Posology and method of administration

Adults (>15 years): 1 tablet once daily.

4.3 Contraindications

Montelukast & Levocetirizine Tablets are contraindicated in patients with known hypersensitivity to Montelukast, levocetirizine, to other piperazine derivatives, or to any of the excipients. Also contradicted in patients with severe renal impairment at less than 10 ml/min creatinine clearance.

4.4 Special warnings 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. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between Montelukast and these underlying conditions has not been established. Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal antiinflammatory agents while taking Montelukast.

Levocetirizine:

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.

Excipients
This medicine contains methyl hydroxybenzoate and propyl hydroxybenzoate which may cause allergic reactions (possibly delayed).

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 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:

Due to the pharmacokinetic, pharmacodynamic and tolerance profile of levocetirizine, no interactions are expected with this antihistamine. Actually, neither pharmacodynamic nor significant pharmacokinetic interaction was reported in drug-drug interactions studies performed, notably with pseudoephedrine or theophylline (400 mg/day).

The extent of absorption of levocetirizine is not reduced with food, although the rate of absorption is decreased.

4.6 Pregnancy and Lactation

Pregnancy

There are no adequate and well controlled studies of either montelukast or levocetirizine in pregnant women. Because animal reproduction studies are not always predictive of human response, this combination should not be used during pregnancy only if it is considered to be clearly essential.

Lactation

It is not known if montelukast is excreted in human milk. Cetirizine has been reported to be excreted in human breast milk. Because levocetirizine is also expected to be excreted in human milk this combination is not recommended during lactation.

Pediatric Use

The safety and effectiveness of levocetirizine in pediatric patients under 2 years of age have not been established.

4.7 Effects on ability to drive and use machines

Montelukast and Levocetirizine Dihydrochloride Tablets is not expected to affect a patient's ability to drive a car or operate machinery. However, in very rare cases, individuals have reported drowsiness or dizziness.

4.8 Undesirable 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, and somnolence. Sometimes, hypersensitivity, irritability, restlessness, insomnia, vomiting and diarrhoea may occur. 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. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

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 consistent with the safety profile in adults and pediatric patients. There were no adverse experiences in the majority of 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 levocetrizine. Should overdose occur, symptomatic or supportive treatment is recommended. Levocetrizine is not effectively removed by dialysis and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested.

5. Pharmacological Particulars

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Montelukast: Drugs For Obstructive Airway Diseases, Levocetirizine Dihydrochloride: Antihistaminic for systemic use.

ATC code: Montelukast: R03DC03, Levocetirizine Dihydrochloride: R06AE09

Montelukast:

The cysteinylleukotrienes (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:

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 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. The safety and efficacy of Montelukast in patients with asthma were demonstrated in clinical trials in which the 10-mg 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 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 postdose 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:

The pharmacokinetics of levocetirizine is linear with dose and time independent with low intersubject 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 0.9 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, N- and 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 faeces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

5.3 Pre-clinical Safety

Montelukast

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, gastrointestinal 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 (>69-fold 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.

Levocetirizine

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

Microcrystalline Cellulose BP

Maize starch BP

Methyl Hydroxybenzoate BP

Propyl Hydroxybenzoate BP

Povidone (PVP K-30) BP

Purified Talc BP

Sodium Starch Glycolate BP

Colloidal Anhydrous Silica BP

Magnesium Stearate BP

Colour Wincoat WT-1129 Yellow IH

Isopropyl Alcohol BP

Dichloromethane BP

Film coating

Titanium dioxide

Ferric oxide yellow

6.2 Incompatibilities

Nil.

6.3 Shelf Life

36 months.

6.4 Special Precautions for storage

Store in dry place below 30°C. Protect from light.

6.5 Nature and contents of container

10 tablets are packed in ALU-ALU blister. Such 3 blisters are packed in one mono carton with insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder

Promed Pharmaceuticals Ltd
P.O. Box 22953-00100
Nairobi, Kenya

8. Marketing Authorisation Number

H2022/CTD9145/20879

9. Date of First Authorisation / Renewal of Authorisation

2022 September 20

10. Date of Revision of the Text

2022 September 20