For PPB use only

1.17 **Summary Product Characteristics (SPC)**

1.17.1 Product Information for Health Professional:

1.1 Product Name: MONTIKAST-4

1.2 Strength: 4 mg

Pharmaceutical Dosage Form : Tablet , Solid Dosage form

2.0 Quality and Quantitative Composition :

2.1 Quality Declaration:

Each uncoated chewable tablet contains:
Montelukast Sodium B.P. Equivalent to Montelukast BP 4 mg
Colour : Tartrazine Yelllow
Excipients QS

2.2 Quantitative Declaration :

Materials	MG
Montelukast Sodium BP Equivalent to Montelukast	4.151
Mannitol BP**	93.509
Crosspovidone BP	5.019
Colour Tartrazine Lake IH	0.226
Aspartame BP	3.019
Low substituted Hydroxy propyl cellulose LH11 BP	3.019
Purified Water as granulating fluid	150.943
Mannitol BP**	50.000
Crosspovidone BP	5.019
Aspartame BP	3.019
Flavour Pineapple 1HS	0.604
Magnesium Stearate BP	2.491

3.0 Pharmaceutical Dosage Form :

Tablet, Solid Dosage form

4.0 Clinical Particulars :

4.1 Therapeutic Indications :

Montelukast is indicated in paediatric patients aged 6 to 14 years in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom 'as-needed' short-acting beta-agonists provide inadequate clinical control of asthma.

Montelukast may also be an alternative treatment option to low-dose inhaled corticosteroids for 6 to 14 years old patients with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled

Montelukast is also indicated in the prophylaxis of asthma from 6 years of age and older in which the predominant component is exercise-induced broncho constriction.

4.2 Posology and method of administration

Posology

The recommended dose for paediatric patients and adolescents 6-14 years of age is one 5 mg chewable tablet daily to be taken in the evening. If taken in connection with food, montelukast should be taken 1 hour before or 2 hours after food. No dosage adjustment within this age group is necessary.

General recommendations:

The therapeutic effect of Montelukast on parameters of asthma control occurs within one day. Patients should be advised to continue taking Montelukast even if their asthma is under control, as well as during periods of worsening asthma.

No dosage adjustment is necessary for patients with renal insufficiency, or mild to moderate hepatic impairment. There are no data on patients with severe hepatic impairment. The dosage is the same for both male and female patients.

Montelukast as an alternative treatment option to low-dose inhaled corticosteroids for mild persistent asthma:

Montelukast is not recommended as monotherapy in patients with moderate persistent asthma. The use of montelukast as an alternative treatment option to low-dose inhaled corticosteroids for children with mild persistent asthma should only be considered for patients who do not have a recent history of serious asthma attacks that required oral corticosteroid use and who have demonstrated that they are not capable of using inhaled corticosteroids . Mild persistent asthma is defined as asthma symptoms more than once a week but less than once a day, nocturnal symptoms more than twice a month but less than once a week, normal lung function between episodes. If satisfactory control of asthma is not achieved at follow-up (usually within one month), the need for an additional or different anti-inflammatory therapy based on the step system for asthma therapy should be evaluated. Patients should be periodically evaluated for their asthma control.

4.3 Contraindications

Therapy with Montelukast in relation to other treatments for asthma:

When treatment with Montelukastis used as add-on therapy to inhaled corticosteroids, Montelukastshould not be

abruptly substituted for inhaled corticosteroids .

Paediatric population

4 mg chewable tablets are available for paediatric patients 2 to 5 years of age.

Method of administration

Oral use

The tablets are to be chewed before swallowing.

4.4 Special Warnings and precaution for use

Patients should be advised never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication for this purpose readily available. If an acute attack occurs, a short-acting inhaled betaagonist should be used. Patients should seek their doctor's advice as soon as possible if they need more inhalations of short-acting beta-agonists than usual.

Montelukast should not be abruptly substituted for inhaled or oral corticosteroids.

There are no data demonstrating that oral corticosteroids can be reduced when montelukast is given concomitantly.

In rare cases, patients on therapy with anti-asthma agents including 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 cases have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been established, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.

Treatment with montelukast does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory drugs.

Montelukast 4 mg Chewable Tablets contains aspartame & Lactose,

4.5 Interaction with other medicinal products and other forms of interactions

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following medicinalproducts: theophylline, prednisone, prednisolone, oral contraceptives (ethinyloestradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.

The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since montelukast is metabolised by CYP 3A4, 2C8,and2C9, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, 2C8,and2C9,such as phenytoin, phenobarbital and rifampicin.

In vitro studies have shown that montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicinal products primarily metabolised by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 *in vivo*. Therefore, montelukast is not anticipated to markedly alter the metabolism of medicinal productsmetabolised by this enzyme (eg., paclitaxel, rosiglitazone, and repaglinide).

Invitro studies have shown that montelukast is asubstrate of CYP2C8,and to a less significant extent, of 2C ,and 3A4. In aclinical drug drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP2C8 and 2C9) gem fibrozil increased the systemic exposure of montelukast by 4.4-fold. No routine dosage adjustment of montelukast is required up on coa dministration with gemfibrozil or other potent inhibitors of CYP2C8,but the physician should be aware of the potential for an increase in adverse reactions.

Based on invitro data,clinically important drug interactions with less potent inhibitors of CYP2C8 (e.g.,trimethoprim) are not anticipated.Co-administration of montelukast with itraconazole,astron ginhibitor of CYP3A4,result edinnosignificant increase in the systemic exposure of montelukast.

4.6 Pregnancy and Lactation

Pregnancy

Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/foetal development.

Limited data from available pregnancy databases do not suggest a causal relationship between Montelukastand
malformations (i.e. limb defects) that have been rarely reported in worldwide post marketing experience.

Montelukastmay be used during pregnancy only if it is considered to be clearly essential.

Breastfeeding

Studies in rats have shown that montelukast is excreted in milk. It is unknown if montelukast is excreted in human milk. Montelukast may be used inbreast-feeding mothers only if it is considered to be clearly essential.

4.7 Effects on ability to drive and use machine :

Montelukast has no or negligible influence on the ability to drive and use machines However individuals have reported drowsiness or dizziness.

4.8 Undesirable Effects

The frequency using the following convention: Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); not known (cannot be estimated from the available data)

Montelukast has been evaluated in clinical studies as follows:

- 10 mg film-coated tablets in approximately 4,000 adult and adolescent asthmatic patients15 years of age and older
- 5 mg chewable tablets in approximately 1,750 paediatric patients and adolescents 6 to 14 years of age, and
- 4 mg chewable tablets in 851 paediatric patients 2 to 5 years of age.

Montelukast has been evaluated in a clinical study in patients with intermittent asthma as follows:

- 4 mg granules and chewable tablets in 1038 paediatric patients 6 months to 5 years of age

The following drug-related adverse reactions in clinical studies were reported commonly (≥1/100 to <1/10) in asthmatic
patients treated with montelukast and at a greater incidence than in patients treated with placebo:

System Organ Class	Adult Patients 15 years and older (two 12-week studies; n=795)	Paediatric Patients 6 to 14 years old (one 8-week study; n=201) (two 56-week studies; n=615)	Paediatric Patients 2 to 5 years old (one 12-week study; n=461) (one 48-week study; n=278)
Nervous system disorders	headache	headache	
Gastrointestinal disorders	abdominal pain		abdominal pain
General disorders and administration site conditions			thirst

With prolonged treatment in clinical trials with a limited number of patients for up to 2 years for adults, and up to 12 months for paediatric patients and adolescents 6 to 14 years of age, the safety profile did not change.

Cumulatively, 502 paediatric patients 2 to 5 years of age were treated with montelukast for at least 3 months, 338 for 6 in these patients either. months or longer, and 534 patients for 12 months or longer. With prolonged treatment, the safety profile did not change

Post-marketing Experience

Adverse reactions reported in post-marketing use are listed, by System Organ Class and specific Adverse Experience

Term, in the table below. Frequency Categories were estimated based on relevant clinical trials.

System Organ Class	Adverse Experience Term	Frequency Category
Infections and infestations	upper respiratory infection†	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
Immune system disorders	hypersensitivity reactions including , anaphylaxis	Uncommon
	hepatic eosinophilic infiltration	Very Rare

Psychiatric disorders	dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor§)	Uncommon
	disturbance in attention, memory , impairment	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality)	Very Rare
Nervous system disorders	dizziness, drowsiness paraesthesia/hypoesthesia, seizure	Uncommon
Cardiac disorders	palpitations	Rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS)	Very Rare
	pulmonary eosinophilia	Very Rare
Gastrointestinal disorders	diarrhoea‡, nausea‡, vomiting‡	Common
	dry mouth, dyspepsia	Uncommon
Hepatobiliary disorders	elevated levels of serum transaminases (ALT, AST)	Common
	hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).	Very Rare
Skin and subcutaneous tissue disorders	rash‡	Common
	bruising, urticaria, pruritus	Uncommon
	angiooedema	Rare
	erythema nodosum, erythema multiforme	Very Rare
Musculoskeletal, connective tissue and bone disorders	arthralgia, myalgia including muscle cramps	Uncommon
General disorders and administration site conditions	pyrexia‡	Common
	asthenia/fatigue, malaise, oedema	Uncommon

*Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), Very Rare (<1/10,000).
†This adverse experience, reported as Very Common in the patients who received montelukast, was also reported as Very Common in the patients who received placebo in clinical trials.
‡This adverse experience, reported as Common in the patients who received montelukast, was also reported as Common in the patients who received placebo in clinical trials.
§ Frequency Category: Rare

4.9 Overdose

In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult patients for 22 weeks and in short-term studies, up to 900 mg/day to patients for approximately one week without clinically important adverse experiences. There have been reports of acute overdose in post-marketing experience and clinical studies with montelukast. These include reports in adults and paediatric patients with a dose as high as 1000 mg (approximately 61 mg/Kg in a 42 month old child). The clinical and laboratory findings observed were consistent with the safety profile in adults and paediatric patients. There were no adverse experiences in the majority of overdose reports.

Symptoms of overdose

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.

Management of overdose

No specific information is available on the treatment of overdose with montelukast.It is not known whether montelukast is dialysable by peritoneal- or haemo-dialysis.

5. Pharmacological Properties

Pharmacotherapeutic group: Other systemic drugs for obstructive airway diseases, Leukotriene receptor antagonists,

ATC Code: RO3D CO3

5.1 Pharmacodynamic Properties

Montelukast is an orally active compound which binds with high affinity and selectivity to the Cys LT1 receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD4 at doses as low as 5 mg. Bronchodilation was observed within two hours of oral administration. The bronchodilation effect caused by a beta-agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adult and paediatric patients. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum) and inperipheral blood while improving clinical asthma control.

Mechanism of action

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 receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

5.2 Pharmacokinetic Properties

Absorption: Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (Cmax) is achieved three hours (Tmax) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and Cmax are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10 mg film-coated tablet was administered without regard to the timing of food ingestion.

For the 5 mg chewable tablet, the Cmax is achieved in two hours after administration in adults in the fasted state. The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.

After administration of the 4 mg chewable tablet to paediatric patients 2 to 5 years of age in the fasted state, Cmax is achieved 2 hours after administration. The mean Cmax is 66% higher while mean Cmin is lower than in adults receiving a 10 mg tablet.

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

Biotransformation: Montelukast is extensively metabolised. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and paediatric patients. Cytochrome P450 2C8isthemajorenzyme in the metabolism of montelukast. Additionally CYP3A4 and2C9 may havea minor contribution,although itraconazole, aninhibitor of CYP3A4,was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10mg montelukast daily.

Based on *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. The contribution of metabolites to the therapeutic effect of montelukast is minimal.

***Elimination*:**

The plasma clearance of montelukast averages 45 ml/min in healthy adults. Following an oral dose of radio labelled montelukast, 86% of the radioactivity was recovered in 5-day faecal 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.

Characteristics in patients:

No dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been undertaken. Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score >9). With high doses of montelukast (20-and 60-fold the recommended adult dose), a decrease in plasma theophylline concentration was observed. This effect was not seen at the recommended dose of 10 mg once daily

5.3 Clinical 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, 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 5,000 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.

6. Pharmaceutical Particulars

6.1 List of Excipients

- Mannitol BP
- Crosspovidone BP
- Colour Tartrazine Lake IH
- Aspartame BP
- Low substituted Hydroxy propyl cellulose LH11 BP
- Flavour Pineapple IHS
- Magnesium Stearate BP

6.2 Incompatibilities: Not Applicable

6.3 Shelf Life: 36 Months

6.4 Special precautions for Storage:

Store in a cool dry place below 30°C.

Keep medicines out of reach of children.

	6.5 Nature and Contents of container 1 X 10 Tablet are packed in carton along with product insert. **7. Marketing Authorization Holder** **Name: PHARMA LIFESCIENCE LTD.** 2 nd Floor, Doctor's Park , 3 Parks Land Nairobi , Kenya P.O.BOX NO. 38148-00623, email-id : Pharmalifescience@outlook.com Telephone No: +254 722 839859 **8. Manufacturer** **Factory : Skybiotech Life Sciences Pvt. Ltd.** Address: Gut No. 5, Gevrai Tanda, Paithan Road, Aurangabad (M.S) India. Country : India Telephone: (91) (240) 2694545 Telefax : (91) (240) 2694488 Email : aher.sr@yahoo.com
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