1. Name of the medicinal product:

Montelukast Tablets BP 10 mg

2. Qualitative and quantitative composition

Each Film coated Tablet contains:

Montelukast Sodium BP Equivalent to Montelukast 10mg

S.No	Ingredients	Specification Standards	Quantity Per tablet (mg)	Function
Blending:				
1.	Montelukast Sodium	USP	10.400	Active Ingredient
2.	Microcrystalline Cellulose (PH 101)	BP	173.600	Diluent
3.	Mannitol	BP	40.000	Binder
4.	Croscarmellose Sodium (AcDiSol)	BP	6.000	Binder
Lubrication:				
5.	Hydroxypropyl Cellulose (Klucel LF)	BP	6.000	Binder
6.	Isopropyl Alcohol BP	BP	50.000	Solvent
7.	Dichloromethane BP #		50.000	Solvent
pre - Lubrication:				
8.	Microcrystalline Cellulose BP (PH102)	BP	20.000	Lubricant
9.	Croscarmellose Sodium BP (AcDiSol)	BP	8.000	Binder
10.	Sodium Lauryl sulphate BP	BP	1.500	Lubricant
Lubrication				
11.	Magnesium Stearate	BP	1.250	Lubricant
Coating				
12.	Opadry Light Yellow YS-1-6382G IHS	IHS	8.000	Coating Agent
13.	Purified Water #	USP	100.000	Aqueous Solvent

Not present in finished product

3. Pharmaceutical form

Oral, film coated tablet.

Pale yellow colored, Circular, biconvex film coated tablets plain on both sides.

4. Clinical particular

4.1 Therapeutic Indications:

Montelukast is indicated in the treatment of asthma as add-on therapy in those patients, with mild to moderate persistentasthma who are inadequately controlled on inhaled corticosteroids and in whom 'as-needed' short acting β-agonistsprovide inadequate clinical control of asthma.

In those asthmatic patients in whom montelukast is indicated in asthma, Montelukast film-coated Tablets can alsoprovide symptomatic relief of seasonal allergic rhinitis.

Montelukast is also indicated in the prophylaxis of asthma in which the predominant component is exercise-inducedbronchoconstriction.

4.2 Posology and method of administration

The dosage for adults and adolescents 15 years of age and older with asthma, or with asthma and concomitant seasonalallergic rhinitis, is one 10-mg tablet daily to be taken in the evening.

General recommendations: The therapeutic effect of montelukast on parameters of asthma control occurs within oneday. Montelukast film-coated Tablets may be taken with or without food. Patients should be advised to continue takingmontelukast even if their asthma is under control, as well as during periods of worsening asthma. Montelukast film-coated Tablets should not be used concomitantly with other products containing the same active ingredient, montelukast.

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

Therapy with Montelukast film-coated Tablets in relation to other treatments for asthma.

Montelukast can be added to a patient's existing treatment regimen.

Inhaled corticosteroids: Treatment with Montelukast can be used as add-on therapy in patients when inhaledcorticosteroids plus "as needed" short acting β-agonists provide inadequate clinical control. Montelukast should not beabruptly substituted for inhaled corticosteroids.

5 mg chewable tablets are available for paediatric patients 6 to 14 years of age.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

The diagnosis of persistent asthma in very young children (6 months – 2 years) should be established by a paediatricianor pulmonologist.

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 β-agonist should be used. Patients should seek their doctors' advice as soon as possible if they need more inhalations ofshort-acting β-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 isoften treated with systemic corticosteroid therapy. These cases usually, but not always, have been associated with thereduction or withdrawal of oral corticosteroid therapy. The possibility that leukotriene receptor antagonists may beassociated with emergence of Churg-Strauss syndrome can neither be excluded nor established. Physicians should bealert 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.

Neuropsychiatric events have been reported in adults, adolescents, and children taking Montelukast film-coated Tablets. Patients and physicians should be alert for neuropsychiatric events. Patients and/or caregivers should be instructed to notify their physician if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with Montelukast film-coated Tablets if such events occur.

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactosemalabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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 onthe pharmacokinetics of the following medicinal products:theophylline, prednisone, prednisolone, oral contraceptives(ethinyl estradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.

The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjectswith co-administration of phenobarbital. Since montelukast is metabolised by CYP 3A4, 2C8 and 2C9, caution should beexercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, 2C8 and 2C9, suchas phenytoin, phenobarbital and rifampicin.

In vitro studies have shown that montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-druginteraction study involving montelukast and rosiglitazone (a probe substrate representative of medicinal productsprimarily 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 products metabolised by this enzyme (eg.,paclitaxel, rosiglitazone, and repaglinide).

In vitro studies have shown that montelukast is a substrate of CYP 2C8, and to a less significant extent, of 2C9, and3A4. In a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and2C9) gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. No routine dosage adjustment ofmontelukast is required upon co-administration with gemfibrozil or other potent inhibitors of CYP 2C8, but the physicianshould be aware of the potential for an increase in adverse reactions.

Based on in vitro data, clinically important drug interactions with less potent inhibitors of CYP 2C8 (e.g., trimethoprim)are not anticipated. Co-administration of montelukast with itraconazole, a strong inhibitor of CYP 3A4, resulted in nosignificant increase in the systemic exposure of montelukast.

4.6 Fertility, 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 montelukast andmalformations (i.e. limb defects) that have been rarely reported in worldwide post marketing experience.

Montelukast may 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 not known if montelukast isexcreted in human milk.

Montelukast may be used in breast-feeding only if it is considered to be clearly essential.

4.7 Effects on ability to drive and use machines

Montelukast 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 has been evaluated in clinical studies in patients with persistent asthma as follows:

• 10 mg film-coated tablets in approximately 4,000 adult and adolescent patients 15 years of age and older.

• 5 mg chewable tablets in approximately 1,750 paediatric patients 6 to 14 years of age.

• 4 mg chewable tablets in 851paediatric patients 2 to 5 years of age, and

• 4 mg granules in 175 paediatric patients 6 months to 2 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 patientstreated with montelukast and at a greater incidence than in patients treated with placebo:

Body System Class	Adult and Adolescent 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	Paediatric Patients 6 months up to 2 year old (one 6-week study; n=175)
Nervous system disorders	headache	headache		hyperkinesia
Respiratory, thoracic, and mediastinal disorders				asthma
Gastrointestinal disorders	abdominal pain		abdominal pain	diarrhoea
Skin and subcutaneous tissue disorders				eczematous dermatitis, rash
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 12months for paediatric patients 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 6months or longer, and 534 patients for 12 months or longer. With prolonged treatment, the safety profile did not changein these patients either. The safety profile in paediatric patients 6 months to 2 years of age did not change with treatmentup to 3 months.

Post-marketing Experience

Adverse reactions reported in post-marketing use are listed, by Sytem Organ Class and specific Adverse ExperienceTerm, in the table below. Frequency Categories were estimated based on the 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 disorder	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), dysphemia	Very Rare
Nervous system disorder	dizziness, drowsiness paraesthesia/hypoesthesia, seizure	Uncommon
Cardiac disorders	palpitations	Rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS) (see section 4.4)	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

No specific information is available on the treatment of overdose with montelukast. In chronic asthma studies,montelukast has been administered at doses up to 200 mg/day to patients for 22 weeks and in short-term studies, up to900 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. Theseinclude reports in adults and children 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. The most frequently occurring adverseexperiences 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 dialysable by peritoneal- or haemo-dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Leukotriene receptor antagonist,

ATC code: R03D C03

Mechanism of action:

The cysteinyl leukotrienes (LTC4, LTD4, LTE4) are potent inflammatory eicosanoids released from various cells includingmast 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 airwaymacrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs havebeen correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects includebronchoconstriction bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment. In allergicrhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactionsand are associated with symptoms of

allergic rhinitis. Intranasal challenge with CysLTs has been shown to increasenasal airway resistance and symptoms of nasal obstruction.

Montelukast is an orally active compound which binds with high affinity and selectivity to the CysLT1 receptor. In clinicalstudies, montelukast inhibits bronchoconstriction due to inhaled LTD4 at doses as low as 5 mg. Bronchodilation wasobserved within 2 hours of oral administration. The bronchodilation effect caused by a β-agonist was additive to thatcaused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due toantigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adult and paediatricpatients. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways as measuredin sputum and peripheral blood while improving clinical asthma control.

In studies in adults, montelukast, 10 mg once daily, compared with placebo, demonstrated significant improvements inmorning FEV1 (10.4% vs 2.7% change from baseline), AM peak expiratory flow rate (PEFR) (24.5 L/min vs 3.3 L/minchange from baseline), and significant decrease in total β-agonist use (-26.1% vs -4.6% change from baseline).Improvement in patient-reported daytime and night-time asthma symptoms scores was significantly better than placebo.

Studies in adults demonstrated the ability of montelukast to add to the clinical effect of inhaled corticosteroid (% changefrom baseline for inhaled beclometasone plus montelukast vs beclometasone, respectively for FEV1: 5.43% vs 1.04%; β-agonist use: -8.70% vs 2.64%). Compared with inhaled beclometasone (200 μg twice daily with a spacer device),montelukast demonstrated a more rapid initial response, although over the 12-week study, beclometasone provided agreater average treatment effect (% change from baseline for montelukast vs beclomethasone, respectively for FEV1:7.49% vs 13.3%; β-agonist use: -28.28% vs -43.89%). However, compared with beclometasone, a high percentage ofpatients treated with montelukast achieved similar clinical responses (e.g., 50% of patients treated with beclometasoneachieved an improvement in FEV1 of approximately 11% or more over baseline while approximately 42% of patientstreated with montelukast achieved the same response).

A clinical study was conducted to evaluate montelukast for the symptomatic treatment of seasonal allergic rhinitis in adultasthmatic patients 15 years of age and older with concomitant seasonal allergic rhinitis. In this study, montelukast 10-mgtablets administered once daily demonstrated a

statistically significant improvement in the Daily Rhinitis Symptomsscore, compared with placebo. The Daily Rhinitis Symptoms score is the average of the Daytime Nasal Symptoms score(mean of nasal congestion, rhinorrhea, sneezing, nasal itching) and the Nighttime Symptoms score (mean of nasalcongestion upon awakening, difficulty going to sleep, and nighttime awakenings scores). Global evaluations of allergic rhinitis by patients and physicians were significantly improved, compared with placebo. The evaluation of asthma efficacywas not a primary objective in this study.

In an 8-week study in paediatric patients 6 to 14 years of age, montelukast 5 mg once daily, compared with placebo,significantly improved respiratory function (FEV1 8.71% vs 4.16% change from baseline; AM PEFR 27.9 L/min vs 17.8L/min change from baseline) and decreased 'as-needed' β-agonist use (-11.7% vs +8.2% change from baseline).

Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults(maximal fall in FEV1 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV144.22 min vs 60.64 min). This effect was consistent throughout the 12-week study period. Reduction in EIB was alsodemonstrated in a short term study in paediatric (maximal fall in FEV1 18.27% vs 26.11%; time to recovery to within 5%of baseline FEV1 17.76 min vs 27.98 min). The effect in both studies was demonstrated at the end of the once-dailydosing interval.

In aspirin-sensitive asthmatic patients receiving concomitant inhaled and/or oral corticosteroids, treatment withmontelukast, compared with placebo, resulted in significant improvement in asthma control (FEV1 8.55% vs -1.74%change from baseline and decrease in total β-agonist use -27.78% vs 2.09% change from baseline).

5.2 Pharmacokinetic properties

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

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

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukastaverages 8-11 litres. Studies in rats with radiolabelled montelukast indicate minimal distribution across the blood-brainbarrier. 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 ofmontelukast are undetectable at steady state in adults and children. Cytochrome P450 2C8 is the major enzyme in themetabolism of montelukast. Additionally CYP 3A4 and 2C9 may have a minor contribution, although itraconazole, aninhibitor of CYP 3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects thatreceived 10 mg montelukast daily. Based on in vitro results in human liver microsomes, therapeutic plasmaconcentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. The contribution ofmetabolites 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 radiolabelledmontelukast, 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 areexcreted 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 withrenal 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 thepharmacokinetics 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 theophyllineconcentration was observed. This effect was not seen at the recommended dose of 10 mg once daily.

5.3 Preclinical safety data

In animal toxicity studies, minor serum biochemical alterations in ALT, glucose, phosphorus and triglycerides wereobserved 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 systemicexposure seen at the clinical dosage. In monkeys, the adverse effects appeared at doses from 150 mg/kg/day (>232-foldthe systemic exposure seen at the clinical dose). In animal studies, montelukast did not affect fertility or reproductiveperformance at systemic exposure exceeding the clinical systemic exposure by greater than 24-fold. A slight decrease inpup 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 seenat systemic exposure >24-fold the clinical systemic exposure seen at the clinical dose. No abnormalities were seen inrats. 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 andrats (15,000 mg/m2 and 30,000 mg/m2 in mice and rats, respectively), the maximum dose tested. This dose is equivalentto 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 500mg/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

Tablet core:

Microcrystalline Cellulose (PH 102)

Mannitol

Croscarmellose Sodium

Sodium Lauryl sulphate

Hydroxypropyl Cellulose

Magnesium Stearate

Opadry Light Yellow YS-1-6382G IHS

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store in the original package below 30°C. Keep out of reach of children.

6.5 Nature and contents of container

Montelukast Tablets BP 10 mg are supplied in box of 2 x 14‘s Blister Packing (Printed Aluminum Foil /clear PVC film).

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

ANNYGOD PHARMA. CO. LTD
28 Ukwulu Street,
Awada Obosi,
Anambra State.
Nigeria.
Mobile: +2348097409264