SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG PRODUCT

Montiget Chewable Tablets 5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains:
Montelukast Sodium USP equivalent to Montelukast….. 5mg

3. PHARMACEUTICAL FORM

White round biconvex shaped tablet engraved "GETZ" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Prophylaxis and chronic treatment of asthma in patients 12 months of age and older.
- Relief of symptoms of allergic rhinitis (AR):
- Seasonal allergic rhinitis (SAR) in patients 2 years of age and older.
- Perennial allergic rhinitis (PAR) in patients 6 months of age and older.
- Acute prevention of exercise-induced bronchoconstriction (EIB) in patients 15 years of age and older.

4.2 Posology and Method of Administration

The therapeutic effect of montelukast sodium on parameters of asthma control occurs within one day. MONTIGET (Montelukast Sodium) tablets, and Pediatric granules can be taken with or without food. Patients should be advised to continue taking the drug while their asthma is controlled as well as during periods of worsened asthma.

MONTIGET (Montelukast Sodium) should be taken once daily. For asthma, the dose should be taken in the evening. For seasonal allergic rhinitis, the time of administration may be individualized to suit patient needs.
Patients with both asthma and seasonal allergic rhinitis should take only one tablet or sachet daily in the evening.

Adults and Adolescents 15 Years of Age and Older with Asthma or Seasonal/Perennial Allergic Rhinitis:
The dosage for adults and adolescents 15 years of age and older is one 10mg tablet daily.

Pediatric patients 6 to 14 years of age with Asthma or Seasonal/Perennial Allergic Rhinitis:
The dosage for pediatric patients 6 to 14 years of age is one 5mg chewable tablet daily.

Pediatric patients 2 to 5 years of age with Asthma or Seasonal/Perennial Allergic Rhinitis:
The dosage for pediatric patients 2 to 5 years of age is one 4mg chewable tablet or one sachet of 4mg granules.

Pediatric patients 12 to 23 months of age with Asthma:
The dosage for pediatric patients 12 to 23 months of age is one sachet of 4mg oral granules.

Pediatric patients 6 to 23 months of age with Perennial Allergic Rhinitis:
The dosage for pediatric patients 6 to 23 months of age is one sachet of 4mg granules.

Exercise-Induced Bronchoconstriction (EIB) in Patients 15 Years of Age and Older:
For prevention of EIB, a single 10mg dose of MONTIGET (Montelukast Sodium) should be taken at least 2 hours before exercise. An additional dose of MONTIGET (Montelukast Sodium) should not be taken within 24 hours of a previous dose. Patients already taking MONTIGET (Montelukast Sodium) daily for another indication (including chronic asthma) should not take an additional dose to prevent EIB. All patients should have available for rescue a short-acting ß-agonist. Safety and effectiveness in patients younger than 15 years of age have not been established. Daily administration of MONTIGET (Montelukast Sodium) for the chronic treatment of asthma has not been established to prevent acute episodes of EIB.

Asthma and Allergic Rhinitis:
Patients with both asthma and allergic rhinitis should take only one MONTIGET (Montelukast Sodium) dose daily in the evening.

Use of MONTIGET (Montelukast Sodium) in relation to other treatment for asthma:
MONTIGET (Montelukast Sodium) can be added to a patient's existing treatment regimen.

Reduction in concomitant therapy
- Bronchodilator Treatment: MONTIGET (Montelukast Sodium) can be added to the treatment of patients who are not adequately controlled on bronchodilator alone. When a clinical response is evident (usually after the first dose), the patient's bronchodilator therapy can be reduced as tolerated.
- Inhaled Corticosteroids: Treatment with MONTIGET (Montelukast Sodium) provides additional clinical benefit to patients treated with inhaled corticosteroids. A reduction in the corticosteroid dose can be made as tolerated. The dose should be reduced gradually with medical supervision. In some patients, the dose of the inhaled corticosteroids can be tapered off completely. MONTIGET (Montelukast Sodium) should not be abruptly substituted for inhaled corticosteroids.

Administration of MONTIGET (Montelukast Sodium) Pediatric granules
MONTIGET (Montelukast Sodium) Pediatric granules 4mg can be administered either directly in the mouth, or mixed with a spoonful of cold or room temperature soft foods. The sachet should not be opened until ready to use. 0After opening the sachet, the full dose (with or without mixing with food) must be administered within 15 minutes. If mixed with food, MONTIGET (Montelukast Sodium) Pediatric granules must not be stored for future use. Discard any unused portion. **MONTIGET (Montelukast Sodium) Pediatric granules are not intended to be dissolved in liquid for administration.** However, liquids may be taken subsequent to administration.

4.3 Contraindications

Montelukast Sodium is contraindicated in a patient who has shown hypersensitivity to the drug or any of its components.
Montelukast sodium is not indicated for use in acute asthma attacks including status asthmaticus.

4.4 Special warnings and special precautions for use

- Montelukast Sodium should not be abruptly substituted for inhaled or oral corticosteroids. However the dose of inhaled corticosteroid may be reduced gradually under medical supervision.
- Although a casual relationship with leukotriene receptor antagonism has not been established, caution and appropriate clinical monitoring is recommended when systemic corticosteroid reduction is considered in patients receiving montelukast sodium.
- Montelukast Sodium should not be used as monotherapy for the treatment and management of exercise-induced asthma. Patients who have exacerbations of asthma after exercise should continue to use their usual regimen of inhaled ß-agonists as prophylaxis and should have it available as and when required.
- Montelukast Sodium does not block bronchoconstrictor response to aspirin or non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients. Such patients should continue to avoid aspirin and other non-steroidal anti-inflammatory drugs.
- Caution should be exercised when using montelukast sodium with bronchodilator therapy. When clinical response is apparent the bronchodilator therapy should be reduced.
- Patients with asthma on therapy with Montelukast sodium may present with systemic eosinophilia. Patients should be reassessed and their treatment regimens should be evaluated.
- Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking Montelukast sodium. Prescribers should carefully evaluate the risks and benefits of continuing treatment with MONTIGET (Montelukast sodium) if such events occur.

4.5 Interaction with other medicaments

Montelukast sodium did not have clinically important effects on the pharmacokinetics of theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/ norethindrone 35/1), terfenadine, digoxin and warfarin.

Phenobarbital
Montelukast sodium when co-administered with phenobarbital the area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40%.

It is recommended that clinical monitoring, particularly in children, be conducted when potent hepatic enzyme inducers such as phenytoin, phenobarbital, or rifampicin are given with montelukast sodium. No dosage adjustment for MONTIGET (montelukast sodium) is recommended.

Gemfibrozil
When montelukast sodium taken with gemfibrozil, increased in the systemic exposure of montelukast occur by 4.4-fold. No routine dosage adjustment of montelukast is required.

Itraconazole
Co-administration of montelukast with itraconazole, resulted in no significant increase in the systemic exposure of montelukast.

4.6 Pregnancy and Lactation

Pregnancy
Montelukast Sodium has not been studied in pregnant women. It should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known if montelukast sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MONTIGET (Montelukast Sodium) is given to a nursing mother.

4.7 Effects on ability to drive and use machine

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 Sodium is generally well tolerated. However, following are the adverse effects reported which usually were mild and did not require discontinuation of therapy.

Most Common:
Stomach pain, stomach or intestinal upset, heartburn, tiredness, fever, stuffy nose, cough, flu, upper respiratory infection, dizziness, headache and rash.

Less Common:
Dry mouth, diarrhea, dyspepsia, nausea, vomiting, hepatic disorders, palpitations, edema, increased bleeding, hypersensitivity reactions (including anaphylaxis, angioedema, and skin reactions), drowsiness, indigestion, tremor, asthenia, dizziness, paraesthesia, hypoesthesia, arthralgia and myalgia.

4.9 Overdosage

Signs and Symptoms:

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.

Treatment:

No specific information is available on the treatment of overdose with montelukast. In the event of overdose, it is reasonable to employ the usual supportive measures; e.g remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required. It is not known whether montelukast is dialyzable by peritoneal- or hemo-dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Anti-asthmatic (Leukotriene receptor antagonist)
ATC Code: R03DC03

Mechanism of Action:
MONTIGET (Montelukast Sodium) is a competitive, selective and orally active leukotriene D4 (cysteinyl leukotriene CysLT1) receptor antagonist. The cysteinyl leukotrienes (LTC4, LTD4, LTE4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors. Binding of cysteinyl leukotrienes to leukotriene receptors has been correlated with the pathophysiology of asthma, including airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process, factors that contribute to the signs and symptoms of asthma. Thus, montelukast sodium inhibits physiologic actions of LTD4 at the CysLT1 receptors, without any agonist activity.

5.2 Pharmacokinetic properties

Absorption:
Montelukast Sodium is rapidly absorbed following oral administration. Peak plasma concentrations of montelukast sodium are achieved in 2 to 4 hours after oral administration. The mean oral bioavailability is 64%.

Distribution:
Montelukast Sodium is more than 99% bound to plasma proteins. The mean plasma half-life of montelukast sodium ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast sodium is nearly linear for oral doses up to 50mg.

Metabolism:
Montelukast Sodium is extensively metabolized in the liver by cytochrome P450 isoenzymes CYP3A4, CYP2A6 and CYP2C9. Therapeutic plasma concentrations of montelukast sodium do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

Elimination:
The plasma clearance of montelukast sodium averages 45mL/min in healthy adults. Montelukast Sodium and its metabolites are excreted principally in the feces via the bile.

Special Populations:
Elderly, Pediatric, males, females, and patients with renal insufficiency have similar plasma pharmacokinetic profiles as young adults.

Hepatic Insufficiency:
Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis has evidence of decreased metabolism and prolonged elimination half life of montelukast sodium resulting in 41% higher mean montelukast sodium area under the plasma concentration curve (AUC) following a single 10mg dose. No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency.

Pediatric Patients
In children 6 to 11 months of age, the systemic exposure to montelukast and the variability of plasma montelukast concentrations were higher than those observed in adults. Safety and tolerability of montelukast in a single-dose pharmacokinetic study in children 6 to 23 months of age were similar to that of patients two years and above.

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 (>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/m^2 and 30,000 mg/m^2 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

- Hydroxy Propyl Cellulose (Klucel LF PHARM)
- Microcrystalline Cellulose (Avicel PH-102)
- Mannitol
- Croscarmellose Sodium
- Aspartame
- Cherry flavor 108B
- Magnesium Stearate

6.2 Incompatibilities

None

6.3 Shelf-life

2 Years
The expiration dates refers to the product correctly stored in the required conditions.

6.4 Special precautions for storage

- Store below 30°C.
- Protect from sunlight & moisture.

6.5 Nature and contents of container

Montiget (Montelukast Sodium) Chewable Tablets 5mg are available in Alu- Alu blister pack of 2 x 7 tablets along with the package insert.

6.6 Special precautions for disposal

No special requirements.

6.7 Instructions for use/handling

- To be dispensed on medical prescription only
- Keep out of the reach of children.

7. MARKETING AUTHORISATION HOLDER

Getz Pharma (Pvt.) Limited
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8. PRODUCT REGISTRATION NUMBER

034837

9. DATE OF PRODUCT REGISTRATION ISSUED

December 20, 2004

10. DATE OF REVISION OF THE TEXT

Nil