**DR. REDDY'S LABORATORIES (PTY) LTD.**
**APPROVED PROFESSIONAL INFORMATION**
**TOPRAZ 4 & 5 (chewable tablets)**
**TOPRAZ 10 (film-coated tablets)**

**SCHEDULING STATUS** S3

## 1 NAME OF THE MEDICINE

TOPRAZ 4, 4 mg, chewable tablet

TOPRAZ 5, 5 mg, chewable tablet

TOPRAZ 10, 10 mg, film-coated tablet

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TOPRAZ 4: Each chewable tablet contains montelukast sodium equivalent to montelukast 4 mg.

TOPRAZ 5: Each chewable tablet contains montelukast sodium equivalent to montelukast 5 mg.

TOPRAZ 10: Each film-coated tablet contains montelukast sodium equivalent to montelukast 10 mg.

TOPRAZ 4 AND 5:

Contain sugar (mannitol).

Contain aspartame.

TOPRAZ 10:

Contain sugar (lactose).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet.

TOPRAZ 4: Light pink to pink coloured, speckled, oval shaped, biconvex tablets debossed with 'MTS' on one side and '4' on the other side.

TOPRAZ 5: Light pink to pink coloured, speckled, round shaped, biconvex tablets debossed with 'MTS' on one side and '5' on the other side.

TOPRAZ 10: Brown coloured, rounded square-shaped, film-coated tablets debossed with 'MTS' on one side and '10' on the other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

TOPRAZ 4 chewable tablets are indicated for paediatric patients 2 to 5 years of age for the prophylaxis and chronic treatment of atopic asthma.

TOPRAZ 5 chewable tablets are indicated for paediatric patients over 6 years of age for the prophylaxis and chronic treatment of atopic asthma.

TOPRAZ 10 film-coated tablets are indicated in adults and children 15 years of age and older for the prophylaxis and chronic treatment of atopic asthma.

In those adult asthmatic patients, in whom TOPRAZ is indicated in asthma, TOPRAZ may also provide some symptomatic relief of seasonal allergic rhinitis.

## 4.2 Posology and method of administration

**TOPRAZ 4 chewable tablets**

*Paediatric patients 2 to 5 years of age with atopic asthma:*

One 4 mg chewable tablet daily.

**TOPRAZ 5 chewable tablets**

*Paediatric patients 6 to 14 years of age with atopic asthma:*

One 5 mg chewable tablet daily.

TOPRAZ 4 mg and 5 mg tablets have not been studied in seasonal allergic rhinitis in children with asthma.

**TOPRAZ 10 film-coated tablets**

*Adults and children 15 years of age and older with atopic asthma with or without seasonal allergic rhinitis:*

One 10 mg film-coated tablet daily.

Clinical studies in adults and children 15 years of age and older did not demonstrate additional clinical benefit to montelukast, as in TOPRAZ at doses above 10 mg daily.

A therapeutic effect of TOPRAZ on parameters of asthma control occurs within one day.

Patients are advised to continue taking TOPRAZ while their asthma is controlled, as well as during periods of worsening asthma.

No dosage adjustment is necessary for the elderly, paediatric patients, for patients with renal insufficiency or mild-to-moderate hepatic impairment

**Therapy with TOPRAZ in relation to other treatments for asthma**

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

*Reduction in Concomitant Therapy*

Bronchodilator Treatments: TOPRAZ can be added to the treatment regimen 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 may be reduced as tolerated.

Inhaled Corticosteroids: A reduction in the corticosteroid dose can be made as tolerated. The dose should be reduced gradually with medical supervision. TOPRAZ should not be abruptly substituted for inhaled corticosteroids.

**Method of administration**

TOPRAZ should be taken once daily in the evening. TOPRAZ can be taken with or without food.

## 4.3 Contraindications

- Hypersensitivity to montelukast or to any other components of TOPRAZ.
- TOPRAZ 4 should not be used in children under the age of 2 years as safety and efficacy have not been demonstrated.

- TOPRAZ 5 should not be used in children under the age of 6 years as safety and efficacy have not been demonstrated.
- TOPRAZ 10 should not be used in children under the age of 15 years.

### 4.4 Special warnings and precautions for use

TOPRAZ is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus as the efficacy of TOPRAZ has not been established for the treatment of acute asthma attacks. Patients should be advised to have appropriate rescue medicine available. Therapy with TOPRAZ can be continued during acute exacerbations of asthma.

Patients should be advised to take TOPRAZ daily as prescribed, even when they are asymptomatic, as well as during periods of worsening asthma, and to contact their medical practitioners if their asthma is not well controlled. Medical attention should be sought if more than the prescribed maximum number of inhalations of short-acting bronchodilator treatment for a 24-hour period, are needed.

TOPRAZ should not be used as monotherapy for the prophylactic treatment of exercise-induced bronchospasm. Patients who have exacerbations of asthma after exercise should continue to use their usual regimen of inhaled beta-agonists as prophylaxis and have available for rescue a short-acting inhaled beta-agonist.

While the dose of inhaled corticosteroid may be reduced gradually under medical supervision TOPRAZ should not be abruptly substituted for inhaled or oral corticosteroids.

**Eosinophilic Conditions**

Patients on therapy with TOPRAZ 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. Medical doctors should be on the alert for patients presenting with eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between TOPRAZ and these underlying conditions has not been established.

**Hypersensitivity to aspirin**

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory (NSAID) medicines while taking TOPRAZ. Although TOPRAZ is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been shown to truncate broncho-constrictor response to aspirin and other non-steroidal anti-inflammatory medicines in aspirin-sensitive asthmatic patients.

**Neuropsychiatric events**

Neuropsychiatric events have been reported in adult, adolescent and paediatric patients taking TOPRAZ.

Post-marketing reports with TOPRAZ use include agitation, aggressive behaviour or hostility, anxiousness, depression, disorientation, disturbance in attention, abnormal dreams, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal ideation and behaviour (including suicide), tic and tremor.

Patients and medical practitioners should be alert for neuropsychiatric events. Patients should

be instructed to notify their medical practitioners if these changes occur. Medical practitioners should carefully evaluate the risks and benefits of continuing treatment with TOPRAZ if such events occur.

**Hepatic impairment**

The metabolism of montelukast may be decreased in patients with mild to moderate hepatic impairment and clinical evidence of cirrhosis. The half-life may be slightly prolonged; however, dosage adjustment is not necessary. No data are available for patients with severe hepatic impairment.

**Renal Insufficiency**

(See section 5.2).

**Use in Elderly**

There are no age-related differences in the efficacy or safety profiles of TOPRAZ.

**Intolerance to excipients**

**TOPRAZ 4 & 5** chewable tablets contain mannitol which may have a laxative effect.

**TOPRAZ 10** film-coated tablets contain lactose. Patients with the rare hereditary conditions of galactose intolerance e.g., galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

**TOPRAZ 4 & 5**

**Phenylalanine**

**Phenylketonurics:**

Phenylketonuric patients should be informed that TOPRAZ 4 & 5 contains phenylalanine (a component of aspartame) 1,2 mg per 4 mg chewable tablet and 1,5 mg per 5 mg chewable tablet. It may be harmful for patients with phenylketonuria.

## 4.5 Interaction with other medicines and other forms of interaction

TOPRAZ may be administered together with other therapies used in the prophylactic treatment of atopic asthma and seasonal allergic rhinitis. In interaction studies, the recommended clinical dose of montelukast as in TOPRAZ did not have clinically important effects on the pharmacokinetics of the following medicines: Theophylline, prednisone, prednisolone, oral contraceptives (ethinyl oestradiol-norethindrone 35 mcg/1 mg), digoxin and warfarin.
The area under the plasma concentration-time curve (AUC) for montelukast was decreased approximately 40 % in subjects with co-administration of phenobarbitone. If co-administration with phenobarbitone, dosage adjustments of TOPRAZ may be necessary. Clinical monitoring is recommended when potent hepatic enzyme inducers such as phenytoin, phenobarbitone or rifampicin, St. John's Wort, or potent hepatic enzyme inhibitors (such as ketoconazole, itraconazole or voriconazole) are given with TOPRAZ.
*In vitro* studies have shown that montelukast is an inhibitor of CYP 2C8. However, data from an interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicine primarily metabolised by CYP 2C8) demonstrated that montelukast doesn't not inhibit CYP 2C8 *in vivo*. Therefore, TOPRAZ is not anticipated to markedly alter the metabolism of

medicines metabolised by this enzyme (e.g., paclitaxel, rosiglitazone and repaglinide, but the doctor should be aware of the potential for an increase in adverse reactions.

*In vitro* studies have shown that montelukast is a substrate of CYP2C8, CYP2C9, and CYP3A4. Data from an interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP2C8 and CYP2C9) demonstrated that gemfibrozil increased the systemic exposure of montelukast by 4,4-fold. Co-administration of itraconazole, a strong CYP3A4 inhibitor, with gemfibrozil and montelukast did not further increase the systemic exposure of montelukast. The effect of gemfibrozil on systemic exposure of montelukast is not considered to be clinically meaningful based on clinical safety data with doses greater than the 10 mg approved dose in adults (e.g., 200 mg/day to adult patients for 22 weeks, and up to 900 mg/day to patients for approximately one week) where clinically important adverse experiences were not observed. Therefore, no dosage adjustment of TOPRAZ is required upon co-administration with gemfibrozil. Based on *in vitro* data, important interactions with other known inhibitors of CYP2C8 (e.g., trimethoprim) are not anticipated. In addition, co-administration of montelukast with itraconazole alone resulted in no significant increase in the systemic exposure of montelukast.

## 4.6 Pregnancy and lactation

### Pregnancy

The safety of TOPRAZ in pregnant and lactating women has not been established.

Available data from published prospective and retrospective cohort studies with montelukast use in pregnant women evaluating major birth defects have not established a drug-associated risk. Available studies have methodologic limitations, including small sample size, in some cases retrospective data collection, and inconsistent comparator groups.

**Breastfeeding**

It is not known if TOPRAZ is excreted in human milk. Women taking TOPRAZ should not breastfeed their babies.

## 4.7 Effects on ability to drive and use machines

As this medicine may cause drowsiness patients are advised not to drive or operate machinery while on this treatment**.**

## 4.8 Undesirable effects

**Infections and infestations**

*Frequent:* Upper respiratory tract infections.

**Blood and the lymphatic system disorders**

*Less frequent:* Increased bleeding tendency, thrombocytopenia.

**Immune system disorders**

*Less frequent:* Hypersensitivity reactions including anaphylaxis, angioedema, hepatic eosinophilic infiltration, systemic eosinophilia (see section 4.5), decreased immune responsiveness.

**Psychiatric disorders**

*Less frequent:* Abnormal dreams, dysphemia (stuttering), [~~and~~] hallucinations, agitation including aggressive behaviour or hostility, anxiousness, depression, disorientation, disturbance in attention, insomnia, memory impairment, obsessive-compulsive symptoms, psychomotor hyperactivity (including irritability, restlessness, and tremor), somnambulism, suicidal thinking and behaviour (suicidality), tic.

**Nervous system disorders**

*Frequent:* Headache.

*Less frequent:* Drowsiness, dizziness, paraesthesia/ hypoaesthesia, seizure.

**Eye disorders**

*Less frequent:* Blepharospasm, mydriasis.

**Ear and labyrinth disorders**

*Less frequent:* vertigo.

**Cardiac disorders**

*Less frequent:* Palpitations, chest pain.

**Respiratory, thoracic and mediastinal disorders**

*Frequent:* Congestion (nasal), cough, influenza.

*Less frequent:* Epistaxis, pulmonary eosinophilia, and Churg-Strauss syndrome.

**Gastrointestinal disorders**

*Less frequent:* Nausea, diarrhoea, vomiting, abdominal pain, bowel movement irregularity, dry mouth, dyspepsia, flatulence, salivary hypersecretion.

**Hepato-biliary disorders**

*Less frequent:* Hepatitis (including cholestatic, hepatocellular and mixed-pattern liver injury).

**Skin and subcutaneous tissue disorders**

*Frequent:* Rash.

*Less frequent:* Pruritus, urticaria, erythema nodosum, erythema multiforme, angioedema, bruising.

**Musculoskeletal, connective tissue and bone disorders**

*Less frequent:* Arthralgia, myalgia including muscle cramps.

**Renal and urinary disorders**

*Less frequent:* Enuresis in children.

**General disorders and administrative site conditions**

*Frequent:* Asthenia, fatigue, fever, increased sweating, abdominal pain, trauma, thirst.

*Less frequent:* Oedema, pyrexia, anaphylaxis.

**Investigations**

*Frequent*: ALT increased, AST increased.

*Less frequent:* Eosinophil count increased, haematocrit decreased, haemoglobin decreased, white blood cell count decreased.

## 4.9 Overdose

No specific information is available on the treatment of overdosage with TOPRAZ.

The most frequent adverse experiences observed were headache, vomiting, thirst, somnolence, psychomotor hyperactivity and abdominal pain.

Treatment is symptomatic and supportive.

It is not known whether montelukast is dialysable by peritoneal or haemodialysis.

## 5 PHARMACOLOGICAL PROPERTIES

**Pharmacological classification:**

A10.2.2 Other anti-asthmatics: Leukotriene receptor antagonist.

### 5.1 Pharmacodynamic properties

Montelukast is a leukotriene receptor antagonist which binds with high affinity and selectivity to the $CysLT_1$ receptor. Montelukast inhibits airway cysteinyl leukotriene receptors, as demonstrated by its ability to inhibit bronchoconstriction due to inhaled LTD4, in asthmatic patients. Montelukast inhibits physiological actions of $LTC_4$, $LTD_4$, and $LTE_4$ at the $CysLT_1$ receptor, without agonist activity.

### 5.2 Pharmacokinetic properties

**Absorption**

Montelukast is absorbed following oral administration.

**4 mg montelukast**

The mean peak plasma concentration ($C_{max}$) for the 4 mg chewable tablet is achieved 2 hours after administration in paediatric patients 2 to 5 years of age in fasted state. Safety and efficacy were demonstrated in clinical studies where the 4 mg chewable tablet was administered without regard to the timing of food ingestion.

**5 mg montelukast**

The mean peak plasma concentration ($C_{max}$) for the 5 mg chewable tablet is achieved 2 hours after administration in adults in the fasted state. The mean oral bioavailability is 73 %.

Food does not have a clinically important influence with chronic administration.

**10 mg montelukast**

The mean peak plasma concentration ($C_{max}$), for the 10 mg film-coated tablet is achieved 3 hours ($T_{max}$), after administration in adults in the fasted state. The mean oral bioavailability is 64 %. A standard meal does not influence the oral bioavailability and $C_{max}$.

**Distribution**

Binding is more than 99 % to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 11 litres.

**Metabolism**

Montelukast is extensively metabolised in the liver.

*In vitro* studies using human liver microsomes indicate that cytochrome P450 isoenzymes CYP3A4 and CYP2C9 are involved in the metabolism of montelukast.

**Elimination**

Elimination data are not available for children 2 to 5 years of age. 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 faecal collections and less than 0,2 % was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates montelukast and its metabolites are excreted almost exclusively via the bile.

The mean plasma half-life of montelukast ranged from 2,7 to 5,5 hours in healthy young adults. Montelukast pharmacokinetics are nearly linear for oral doses up to 50 mg. No difference in pharmacokinetics was noted between dosing in the morning or in the evening. During once daily dosing there is little accumulation of the parent drug in plasma (approximately 14 %).

**Special populations**

**Hepatic insufficiency**

Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in approximately 41 % higher mean montelukast area under the plasma concentration curve (AUC) following a single 10 mg dose. The elimination of montelukast is slightly prolonged compared with that in healthy subjects (mean half-life, 7,4 hours). No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score greater than 9).

**Renal Insufficiency**

Since montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of montelukast were not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.

**Elderly**

The pharmacokinetic profile and the oral bioavailability of a single 10 mg oral dose of montelukast are similar in elderly and younger adults. The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

The other ingredients in TOPRAZ 4 and TOPRAZ 5 chewable tablets are mannitol, hydroxypropyl cellulose, croscarmellose sodium, ferric oxide, cherry flavour, aspartame, microcrystalline cellulose and magnesium stearate.

The other ingredients in TOPRAZ 10 film-coated tablets are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, hypromellose, titanium dioxide, macrogol, iron oxide yellow, iron oxide red and iron oxide black.

### 6.2 Incompatibilities

Not Applicable

### 6.3 Shelf-life

2 years

### 6.4 Special precautions for storage

Store at or below 25 °C protected from moisture and light.

Keep the blisters in the carton until required for use.

Keep the HDPE containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

### 6.5 Nature and contents of container

TOPRAZ 4, 5 and 10 are available in packs of 14/28/30/100 tablets in white HDPE containers with white plastic lids and in packs of 10 tablets in blisters, one side silver coloured aluminium foil and the other side blue coloured aluminium foil with a polyethylene layer containing desiccant.

### 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 HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

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## 8 REGISTRATION NUMBERS

TOPRAZ 4: 43/10.2.2/0785

TOPRAZ 5: 43/10.2.2/0786

TOPRAZ 10: 43/10.2.2/0787

## 9 DATE OF FIRST AUTHORISATION

30 September 2011

## 10 DATE OF REVISION OF THE TEXT

24 November 2022