

**SCHEDULING STATUS**

S3

**PROPRIETARY NAME (AND DOSAGE FORM)**

**TOPRAZ 4** (chewable tablet)

**TOPRAZ 5** (chewable tablet)

**TOPRAZ 10** (film-coated tablet)

**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.

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.

Chewable 4 and 5 mg tablets: Contain sugar (mannitol).

Chewable 4 and 5 mg tablets: Contain aspartame.

Film-coated 10 mg tablets: Contain sugar (lactose).

## **PHARMACOLOGICAL CLASSIFICATION**

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

## **PHARMACOLOGICAL ACTION**

### **Pharmacodynamic properties**

Montelukast is a leukotriene receptor antagonist which binds with high affinity and selectivity to the CysLT<sub>1</sub> receptor. Montelukast inhibits airway cysteinyl leukotriene receptors, as demonstrated by its ability to inhibit bronchoconstriction due to inhaled LTD<sub>4</sub>, in asthmatic patients. Montelukast inhibits physiological actions of LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub> at the CysLT<sub>1</sub> receptor, without agonist activity.

### **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

**Dr. Reddy's Laboratories (Pty) Ltd.**  
**APPROVED PACKAGE INSERT**

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 %).

**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-

**Dr. Reddy's Laboratories (Pty) Ltd.  
APPROVED PACKAGE INSERT**

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.

**INDICATIONS**

**TOPRAZ** tablets are indicated for prophylactic treatment of atopic asthma.

**TOPRAZ 4** chewable tablets are indicated for paediatric patients 2 to 5 years of age.

**TOPRAZ 5** chewable tablets are indicated for paediatric patients over 6 years of age.

**TOPRAZ 10** film-coated tablets are indicated in adults and children 15 years of age and older.

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

**CONTRAINDICATIONS**

- Hypersensitivity to montelukast or to any other components of **TOPRAZ**.
- Pregnancy and lactation (see Pregnancy and lactation).
- **TOPRAZ 5** should not be used in children under the age of 6 years as safety and efficacy

**Dr. Reddy's Laboratories (Pty) Ltd.**  
**APPROVED PACKAGE INSERT**

have not been demonstrated.

- **TOPRAZ 4** should not be used in children under the age of 2 years as safety and efficacy have not been demonstrated.
- **TOPRAZ 10** should not be used in children under the age of 15 years.

**WARNINGS AND SPECIAL PRECAUTIONS**

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

**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.

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.

Patients should be advised that, while using **TOPRAZ**, medical attention should be sought if short-acting inhaled bronchodilators are needed more often than usual, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for 24-hour period are needed.

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

**Dr. Reddy's Laboratories (Pty) Ltd.  
APPROVED PACKAGE INSERT**

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 alert to 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.

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory 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.

**Renal Insufficiency**

(See Pharmacokinetic properties).

**Use in Elderly**

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

**Ability to drive and operate machinery**

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

**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.

**Dr. Reddy's Laboratories (Pty) Ltd.  
APPROVED PACKAGE INSERT**

**TOPRAZ 4 & 5**

**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.

**INTERACTIONS**

**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

**Dr. Reddy's Laboratories (Pty) Ltd.  
APPROVED PACKAGE INSERT**

increase in adverse reactions.

**PREGNANCY AND LACTATION**

**TOPRAZ** should not be used in pregnancy and lactation (see CONTRAINDICATIONS).

**Congenital limb defects have been reported in the offspring of women being treated with TOPRAZ during pregnancy. A causal relationship between these events and TOPRAZ has not been established.**

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

**DOSAGE AND DIRECTIONS FOR USE**

**TOPRAZ** should be taken once daily in the evening.

**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

**Dr. Reddy's Laboratories (Pty) Ltd.  
APPROVED PACKAGE INSERT**

*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.

**TOPRAZ** can be taken with or without food.

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, for patients with renal insufficiency or mild-to-moderate hepatic impairment or for patients of either gender.

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

## **SIDE-EFFECTS**

### **Blood and the lymphatic system disorders**

*Less frequent:* Increased bleeding tendency.

### **Immune system disorders**

*Less frequent:* Hypersensitivity reactions including anaphylaxis, angioedema, hepatic eosinophilic infiltration, systemic eosinophilia (see WARNINGS AND SPECIAL PRECAUTIONS).

### **Psychiatric disorders**

*Less frequent:* Abnormal dreams and hallucinations, agitation including aggressive behaviour, anxiousness, depression, insomnia, irritability, restlessness, suicidal thinking and behaviour

**Dr. Reddy's Laboratories (Pty) Ltd.  
APPROVED PACKAGE INSERT**

(suicidality), tremor.

**Nervous system disorders**

*Frequent:* Headache, vertigo.

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

**Cardiac disorders**

*Less frequent:* Palpitations, chest pain.

**Respiratory, thoracic and mediastinal disorders**

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

*Less frequent:* Epistaxis.

**Gastrointestinal disorders**

*Frequent:* Dyspepsia, gastroenteritis (infectious), pain (dental), diarrhoea, thirst, abdominal pain.

*Less frequent:* Nausea, vomiting.

**Hepato-biliary disorders**

*Less frequent:* Cholestatic hepatitis.

**Skin and subcutaneous tissue disorders**

*Frequent:* Rash.

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

**Musculoskeletal, connective tissue and bone disorders**

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

**General disorders and administrative site conditions**

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

*Less frequent:* Oedema, pyrexia, anaphylaxis.

**Investigations**

**Dr. Reddy's Laboratories (Pty) Ltd.  
APPROVED PACKAGE INSERT**

*Frequent:* ALT increased, AST increased, pyuria.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**

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

The most frequent adverse experiences observed were thirst, somnolence, mydriasis, hyperkinesias and abdominal pain.

Treatment is symptomatic and supportive.

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

**IDENTIFICATION**

**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.

**PRESENTATION**

**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.

**STORAGE INSTRUCTIONS**

**Dr. Reddy's Laboratories (Pty) Ltd.  
APPROVED PACKAGE INSERT**

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.

**REGISTRATION NUMBERS**

**TOPRAZ 4:** 43/10.2.2/0785

**TOPRAZ 5:** 43/10.2.2/0786

**TOPRAZ 10:** 43/10.2.2/0787

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF  
REGISTRATION**

Dr. Reddy's Laboratories (Pty) Ltd.

Third Floor, The Place

1 Sandton Drive

Sandton

2196

**DATE OF PUBLICATION OF THE PACKAGE INSERT**

Date of registration: 30 September 2011

Date of revision: 02 June 2017

**Dr. Reddy's Laboratories (Pty) Ltd.  
APPROVED PACKAGE INSERT**