PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

TOPRAZ DUO 10 mg/5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg montelukast (as montelukast sodium) and 5 mg levocetirizine dihydrochloride.

Excipients with known effect:

Each film-coated tablet contains 83,3 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Light yellow to yellow coloured, round shaped, bevelled edge, biconvex, film-coated tablets, debossed with “ML” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of symptoms associated with allergic rhinitis (seasonal and perennial) in adults.

4.2 Posology and method of administration

Posology

Adults (≥ 18 years of age):

The recommended dose is one (1) tablet daily in the evening.

Special populations

Renal impairment:

No dose adjustment is needed in patients with mild renal impairment (creatinine clearance > 79 mL/min). TOPRAZ DUO should be used with caution and under strict medical supervision in patients with moderate to severe renal impairment (creatinine clearance < 79 mL/min to > 10 mL/min).

Hepatic impairment:

No dose adjustment is needed in patients with hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of the dose is recommended (see *Renal impairment* above).

Paediatric population:

The safety and efficacy of TOPRAZ DUO in adolescents under the age of 18 years have not been established. TOPRAZ DUO should not be used in adolescents under 18 years.

Method of administration

Orally.

Swallow the tablet with liquid.

The tablet can be taken with or without food.

Duration of use:

Intermittent allergic rhinitis (symptoms experienced for less than four days a week or for less than four weeks a year) must be treated according to the disease and its history; it can be stopped once the symptoms have disappeared and can be restarted again when symptoms reappear. In case of persistent allergic rhinitis (symptoms experienced for more than four days a week or for more than four weeks a year), continuous therapy can be proposed to the patient during the period of

exposure to allergens.

4.3 Contraindications

- Hypersensitivity to montelukast, levocetirizine dihydrochloride, cetirizine, hydroxyzine, any other piperazine derivatives or to any of the excipients listed in section 6.1.
- End-stage renal failure (creatinine clearance < 10 mL/min) (see section 4.2, Renal impairment).

4.4 Special warnings and precautions for use

MONTELUKAST

Acute asthma attacks

TOPRAZ DUO is not indicated in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus, as the efficacy of TOPRAZ DUO has not been established for the treatment of acute asthma attacks.

Patients should be advised never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medicine 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 of short-acting β-agonists than usual.

Oral corticosteroids

Montelukast should not be substituted abruptly for inhaled or oral corticosteroids. There are no data demonstrating that oral corticosteroids can be reduced when montelukast is given concomitantly.

Eosinophilic conditions

In rare cases, patients on therapy with anti-asthma medicines, 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

(see section 4.8). These cases have sometimes been associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been established, medical practitioners 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.

Aspirin sensitivity

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

LEVOCETIRIZINE DIHYDROCHLORIDE

Alcohol consumption

Precaution is recommended with concurrent intake of alcohol (see section 4.5, LEVOCETIRIZINE DIHYDROCHLORIDE).

Urinary retention

Caution should be taken in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as levocetirizine may increase the risk of urinary retention.

Epilepsy

Caution should be taken in patients with epilepsy and patients at risk of convulsions as levocetirizine may cause seizure aggravation.

Allergy skin tests

Response to allergy skin tests is inhibited by antihistamines and a wash-out period (3 days) is required before performing them.

Effects when treatment is stopped

Pruritus may occur when levocetirizine is stopped even if those symptoms were not present before treatment initiation. The symptoms may resolve spontaneously. In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.

TOPRAZ DUO

Lactose monohydrate:

TOPRAZ DUO contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take TOPRAZ DUO.

4.5 Interaction with other medicines and other forms of interaction

MONTELUKAST

Montelukast may be administered with other medicines 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 medicines: theophylline, prednisone, prednisolone, oral contraceptives (ethinylestradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.

CYP3A4, 2C8 and 2C9 inducers

The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40 % in subjects with co-administration of phenobarbital (phenobarbitone). Since montelukast is metabolised by CYP3A4, 2C8 and 2C9, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP3A4, 2C8 and 2C9, such as phenytoin, phenobarbital and rifampicin.

Medicines metabolised by CYP2C8

In vitro studies have shown that montelukast is a potent inhibitor of CYP2C8. However, data from a drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicines primarily metabolised by CYP2C8) demonstrated that montelukast does not inhibit CYP2C8 *in vivo*. Therefore, montelukast is not anticipated to markedly alter the metabolism of medicines metabolised by this enzyme (e.g. paclitaxel, rosiglitazone and repaglinide).

Gemfibrozil

In vitro studies have shown that montelukast is a substrate of CYP2C8 and to a less significant extent, of CYP2C9 and 3A4.

In a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP2C8 and 2C9), gemfibrozil increased the systemic exposure of montelukast by 4,4-fold. No routine dosage adjustment of montelukast is required upon co-administration with gemfibrozil or other potent inhibitors of CYP2C8, but the health care provider should be aware of the potential for an increase in adverse reactions.

Itraconazole

Based on *in vitro* data, clinically important drug interactions with less potent inhibitors of CYP2C8 (e.g. trimethoprim) are not anticipated. Co-administration of montelukast with itraconazole, a strong inhibitor of CYP3A4, resulted in no significant increase in the systemic exposure of montelukast.

LEVOCETIRIZINE DIHYDROCHLORIDE

No interaction studies have been performed with levocetirizine (including no studies with CYP3A4 inducers).

Studies with the racemate compound cetirizine demonstrated that there were no clinically relevant adverse interactions with antipyrine, azithromycin, cimetidine, diazepam, erythromycin, glipizide, ketoconazole and pseudoephedrine.

Theophylline

A small decrease in the clearance of cetirizine (16 %) was observed with theophylline (400 mg once a day), while the disposition of theophylline was not altered by concomitant cetirizine administration.

Ritonavir

In a multiple dose study of ritonavir (600 mg twice daily) and cetirizine (10 mg daily), the extent of exposure to cetirizine was increased by about 40 % while the disposition of ritonavir was slightly altered (-11 %) further to concomitant cetirizine administration.

Food

The extent of absorption of levocetirizine is not reduced with food, although the rate of absorption is decreased.

Alcohol

In sensitive patients, the concurrent administration of cetirizine or levocetirizine and alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of montelukast and levocetirizine in pregnant women has not been established. Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/fetal development. Animal reproduction studies are not always predictive of human response.
TOPRAZ DUO should not be used during pregnancy.

Breastfeeding

The safety of montelukast and levocetirizine in breastfeeding women has not been established. It is not known if montelukast is excreted in human breast milk. Cetirizine, the racemate of levocetirizine, has been reported to be excreted in human breast milk. Therefore, the excretion of levocetirizine in human breast milk is likely.

TOPRAZ DUO should not be used during breastfeeding.

Fertility

There are no fertility data available.

4.7 Effects on ability to drive and use machines

TOPRAZ DUO may cause side effects, such as dizziness and drowsiness and can affect the ability to drive a vehicle and use machines (see section 4.8). Caution is advised before driving a vehicle or operating machinery until the effects of TOPRAZ DUO are known.

4.8 Undesirable effects

MONTELUKAST

Summary of the safety profile

Headache and abdominal pain are adverse reactions frequently experienced while taking montelukast.

Tabulated list of adverse reactions

Infections and infestations:

Frequent: Upper respiratory infection.

Blood and lymphatic system disorders:

Less frequent: Increased bleeding tendency, thrombocytopenia, hepatic eosinophilic infiltration.

Immune system disorders:

Less frequent: Hypersensitivity reactions including anaphylaxis, angioedema.

Metabolism and nutrition disorders:

Less frequent: Oedema.

Psychiatric disorders:

Less frequent: Dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor), disturbance in attention, memory impairment, tic, hallucinations, disorientation, suicidal thinking and behaviour (suicidality).

Nervous system disorders:

Less frequent: Dizziness, drowsiness, paraesthesia/hypaesthesia, seizure.

Cardiac disorders:

Less frequent: Palpitations.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Epistaxis, Churg-Strauss syndrome (CSS) (see section 4.4), pulmonary eosinophilia.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting.

Less frequent: Dry mouth, dyspepsia.

Hepato-biliary disorders:

Frequent: Elevated serum transaminases (ALT, AST) levels.

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

Skin and subcutaneous tissue disorders:

Frequent: Rash.

Less frequent: Bruising, urticaria, pruritus, erythema nodosum, erythema multiforme.

Musculoskeletal and connective tissue disorders:

Less frequent: Arthralgia, myalgia including muscle cramps.

Renal and urinary disorders:

Less frequent: Enuresis in children.

General disorders and administration site conditions:

Frequent: Pyrexia.

Less frequent: Asthenia/fatigue, malaise.

LEVOCETIRIZINE DIHYDROCHLORIDE

Tabulated list of adverse reactions

Nervous system disorders:

Frequent: Headache, somnolence.

Gastrointestinal disorders:

Frequent: Dry mouth.

Less frequent: Abdominal pain.

General disorders and administration site conditions:

Frequent: Fatigue.

Less frequent: Asthenia.

Post-marketing experience

Immune system disorders:

Frequency unknown: Hypersensitivity including anaphylaxis.

Metabolism and nutrition disorders:

Frequency unknown: Increased appetite.

Psychiatric disorders:

Frequency unknown: Aggression, agitation, hallucinations, depression, insomnia, suicidal ideation.

Nervous system disorders:

Frequency unknown: Convulsions, paraesthesia, dizziness, syncope, tremor, dysgeusia.

Eye disorders:

Frequency unknown: Visual disturbances, blurred vision.

Ear and labyrinth disorders:

Frequency unknown: Vertigo.

Cardiac disorders:

Frequency unknown: Palpitations, tachycardia.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Dyspnoea.

Gastrointestinal disorders:

Frequency unknown: Nausea, vomiting, diarrhoea.

Hepato-biliary disorders:

Frequency unknown: Hepatitis.

Skin and subcutaneous tissue disorders:

Frequency unknown: Angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria.

Musculoskeletal and connective tissue:

Frequency unknown: Myalgia, arthralgia.

Renal and urinary disorders:

Frequency unknown: Dysuria, urinary retention.

General disorders and administration site conditions:

Frequency unknown: Oedema.

Investigations:

Frequency unknown: Increased body mass, abnormal liver function tests.

Description of selected adverse reactions

After levocetirizine discontinuation, pruritus has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of TOPRAZ DUO is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are

requested to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

MONTELUKAST

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

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.

Management of overdose

Should overdose occur, symptomatic and supportive treatment is recommended.

LEVOCETIRIZINE DIHYDROCHLORIDE

Symptoms

Symptoms of overdose may include drowsiness in adults.

In children, agitation and restlessness may initially occur, followed by drowsiness.

Management of overdose

There is no known specific antidote to levocetirizine.

Should overdose occur, symptomatic or supportive treatment is recommended. Levocetirizine is not effectively removed by haemodialysis. Activated charcoal may be administered orally within the first hour post overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.7.1 Antihistaminics.

Pharmacotherapeutic group: Montelukast, combinations.

ATC code: R03DC53.

MONTELUKAST

Pharmacotherapeutic group: Leukotriene receptor antagonist.

ATC code: R03DC03.

Mechanism of action

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene (CysLT) receptors.

The CysLT type-1 ($CysLT_1$) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include bronchoconstriction, mucous secretion, vascular permeability and eosinophil recruitment. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction.

Pharmacodynamic effects

Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD_4 at doses as low as 5 mg. Bronchodilation was observed within 2 hours of oral administration. The bronchodilation effect caused by a β-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 in peripheral blood while improving clinical asthma control.

Clinical efficacy and safety

In studies in adults, montelukast 10 mg once daily, compared with placebo, demonstrated significant improvements in morning FEV_1 (10,4 % vs 2,7 % change from baseline), AM peak expiratory flow rate (PEFR) (24,5 L/min vs 3,3 L/min change 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 (% change from baseline for inhaled beclomethasone plus montelukast vs beclomethasone, respectively for FEV_1: 5,43 % vs 1,04 %; β-agonist use: -8,70 % vs 2,64 %). Compared with inhaled beclomethasone (200 µg twice daily with a spacer device), montelukast demonstrated a more rapid initial response, although over the 12-week study, beclomethasone provided a greater average treatment effect (% change from baseline for montelukast vs beclomethasone, respectively for FEV_1: 7,49 % vs 13,3 %; β-agonist use: -28,28 % vs -43,89 %). However, compared with beclomethasone, a high percentage of patients treated with montelukast achieved similar clinical responses (e.g. 50 % of patients treated with beclomethasone achieved an improvement in FEV_1 of approximately 11 % or more over baseline while approximately 42 % of patients treated with montelukast achieved the same response).

A clinical study was conducted to evaluate montelukast for the symptomatic treatment of seasonal allergic rhinitis in adult and adolescent asthmatic patients 15 years of age and older with concomitant seasonal allergic rhinitis. In this study, montelukast 10 mg tablets administered once daily demonstrated a statistically significant improvement in the Daily Rhinitis Symptoms score, compared with placebo. The Daily Rhinitis Symptoms score is the average of the Daytime Nasal

Symptoms score (mean of nasal congestion, rhinorrhoea, sneezing, nasal itching) and the Night-Time Symptoms score (mean of nasal congestion upon awakening, difficulty going to sleep and night-time awakenings scores). Global evaluations of allergic rhinitis by patients and medical practitioners were significantly improved, compared with placebo. The evaluation of asthma efficacy was 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 (FEV_1 8,71 % vs 4,16 % change from baseline; AM PEFR 27,9 L/min vs 17,8 L/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 FEV_1 22,33 % for montelukast vs 32,40 % for placebo; time to recovery to within 5 % of baseline FEV_1 44,22 min vs 60,64 min). This effect was consistent throughout the 12-week study period. Reduction in EIB was also demonstrated in a short-term study in paediatric patients (maximal fall in FEV_1 18,27 % vs 26,11 %; time to recovery to within 5 % of baseline FEV_1 17,76 min vs 27,98 min). The effect in both studies was demonstrated at the end of the once-daily dosing interval.

In aspirin-sensitive asthmatic patients receiving concomitant inhaled and/or oral corticosteroids, treatment with montelukast, compared with placebo, resulted in significant improvement in asthma control (FEV_1 8,55 % vs -1,74 % change from baseline and decrease in total β-agonist use -27,78 % vs 2,09 % change from baseline).

LEVOCETIRIZINE DIHYDROCHLORIDE

Pharmacotherapeutic group: Antihistamine for systemic use, piperazine derivatives.

ATC code: R06AE09.

Mechanism of action

Levocetirizine, the (*R*) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H_1 receptors. Binding studies revealed that levocetirizine has high affinity for human H_1 receptors

(Ki = 3,2 nmol/L). Levocetirizine has an affinity 2-fold higher than that of cetirizine (Ki = 6,3 nmol/L). Levocetirizine dissociates from H_1 receptors with a half-life of 115 ± 38 min.

After single administration, levocetirizine shows a receptor occupancy of 90 % at 4 hours and 57 % at 24 hours.

Pharmacodynamic studies in healthy volunteers demonstrate that, at half the dose, levocetirizine has comparable activity to cetirizine, both in the skin and in the nose.

Pharmacodynamic effects

The pharmacodynamic activity of levocetirizine has been studied in randomised, controlled trials: In a study comparing the effects of levocetirizine 5 mg, desloratadine 5 mg and placebo on histamine-induced wheal and flare, levocetirizine treatment resulted in significantly decreased wheal and flare formation which was highest in the first 12 hours and lasted for 24 hours, ($p < 0,001$) compared with placebo and desloratadine.

The onset of action of levocetirizine 5 mg in controlling pollen-induced symptoms have been observed at 1 hour after medicine intake in placebo-controlled trials in the model of the allergen challenge chamber.

In vitro studies (Boyden chambers and cell layers techniques) show that levocetirizine inhibits eotaxin-induced eosinophil transendothelial migration through both dermal and lung cells. A pharmacodynamic experimental study *in vivo* (skin chamber technique) showed three main inhibitory effects of levocetirizine 5 mg in the first 6 hours of pollen-induced reaction, compared with placebo in 14 adult patients: inhibition of VCAM-1 release, modulation of vascular permeability and a decrease in eosinophil recruitment.

5.2 Pharmacokinetic properties

MONTELUKAST

Absorption

Montelukast is rapidly absorbed following oral administration. The mean peak plasma concentration (C_{max}) is achieved 3 hours (T_{max}) after administration in adults in the fasted state. The

mean oral bioavailability is 64 %. The oral bioavailability and C_{max} are not influenced by a standard meal.

Distribution

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

Biotransformation

Montelukast is extensively metabolised. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and children. Cytochrome P450 isozyme 2C8 is the major enzyme in the metabolism of montelukast. Additionally, CYP3A4 and 2C9 may have a minor contribution, although itraconazole, an inhibitor of CYP3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10 mg montelukast daily. Based on *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P4503A4, 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 radiolabelled 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.

Special populations

Elderly population

No dosage adjustment is necessary for elderly patients.

Renal impairment

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.

Hepatic impairment

No dosage adjustment is necessary for elderly patients or patients with mild to moderate hepatic insufficiency. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score > 9).

LEVOCETIRIZINE DIHYDROCHLORIDE

The pharmacokinetics of levocetirizine are linear with dose- and time-independent, with low intersubject variability. The pharmacokinetic profile is the same when given as the single enantiomer or when given as cetirizine. No chiral inversion occurs during the process of absorption and elimination.

Absorption

Levocetirizine is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0,9 h after dosing. Steady state is achieved after two days. Peak concentrations are typically 270 ng/mL and 308 ng/mL following a single and a repeated 5 mg once daily dose, respectively. The extent of absorption is dose-independent and is not altered by food, but the peak concentration is reduced and delayed.

Distribution

No tissue distribution data are available in humans, neither concerning the passage of levocetirizine through the blood-brain barrier. Levocetirizine is 90 % bound to plasma proteins. The distribution of levocetirizine is restrictive, as the volume of distribution is 0,4 L/kg.

Biotransformation

The extent of metabolism of levocetirizine in humans is less than 14 % of the dose and therefore differences resulting from genetic polymorphism or concomitant intake of enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, *N*- and *O*-dealkylation and taurine conjugation. Dealkylation pathways are primarily mediated by CYP3A4 while aromatic oxidation involved multiple and/or unidentified CYP isoforms. Levocetirizine had no effect on the activities of CYP isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 at concentrations well above peak concentrations achieved following a 5 mg oral dose.

Due to its low metabolism and absence of metabolic inhibition potential, the interaction of levocetirizine with other substances, or vice versa, is unlikely.

Elimination

The plasma half-life in adults is 7,9 ± 1,9 hours. The half-life is shorter in small children. The mean apparent total body clearance in adults is 0,63 mL/min/kg. The major route of excretion of levocetirizine and metabolites is via urine, accounting for a mean of 85,4 % of the dose. Excretion via faeces accounts for only 12,9 % of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

Special populations

Renal impairment:

The apparent body clearance of levocetirizine is correlated to the creatinine clearance. It is therefore recommended to adjust the dosing intervals of levocetirizine, based on creatinine clearance in patients with moderate and severe renal impairment. In anuric end-stage renal disease subjects, the total body clearance is decreased by approximately 80 % when compared to normal subjects. The amount of levocetirizine removed during a standard 4-hour haemodialysis procedure was < 10 %.

Elderly patients:

Limited pharmacokinetic data are available in elderly subjects. Following once daily repeat oral administration of 30 mg levocetirizine for 6 days in 9 elderly subjects (65 – 74 years of age), the total body clearance was approximately 33 % lower compared to that in younger adults. The disposition of racemic cetirizine has been shown to be dependent on renal function rather than on age. This finding would also be applicable for levocetirizine, as levocetirizine and cetirizine are both predominantly excreted in urine. Therefore, the levocetirizine dose should be adjusted in accordance with renal function in elderly patients.

Hepatic impairment:

The pharmacokinetics of levocetirizine in hepatically impaired subjects have not been tested. Patients with chronic liver diseases (hepatocellular, cholestatic and biliary cirrhosis) given 10 mg or 20 mg of the racemic compound cetirizine as a single dose had a 50 % increase in half-life along with a 40 % decrease in clearance compared to healthy subjects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Croscarmellose sodium

Hydroxypropyl cellulose

Lactose monohydrate

Microcrystalline cellulose

Magnesium stearate.

Tablet coating

Opadry Yellow 20A82772:

Hypromellose

Hydroxypropyl cellulose

Titanium dioxide (E171)

Iron oxide yellow (E172)

Iron oxide red (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from moisture.

Keep blister strips in outer carton until required for use.

6.5 Nature and contents of container

Aluminium/PVC blister strip containing 7 or 10 tablets. 4 blister strips containing 7 tablets, or 3 blister strips containing 10 tablets are packed in an outer cardboard carton.

Pack sizes: 28 and 30.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park, Building B, Ground Floor

22 Karee Street

Centurion

Pretoria 0157

Tel: 012 748 6400

8. REGISTRATION NUMBER

61/5.7.1/1427

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

12 May 2026

10. DATE OF REVISION OF THE TEXT

Not applicable.