30XXXXX

MONTELUKAST
LEVOCETIRIZINE HCl

℞

CO-ALTRIA®

10mg / 5mg Tablet

Leukotriene Receptor Antagonist / Antihistamine

FORMULATION

Each uncoated bilayered tablet contains:
Montelukast (as sodium), USP.....10mg
Levocetirizine hydrochloride, USP.....5mg

DESCRIPTION

Circular, flat, beveled edge, plain, uncoated bilayered tablets, of which one layer is light yellow to creamish yellow and the other layer is light pink to pink coloured, with slight mottled appearance on both the layers.

INDICATIONS

Indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis.

CONTRAINDICATIONS

Co-Altria Tablets are contraindicated in patients with known hypersensitivity to montelukast, levocetirizine, to other piperazine derivatives or to any of the excipients. Also, contraindicated in patients with severe renal impairment at less than 10 mL/min creatinine clearance, and patients undergoing hemodialysis.

DOSAGE AND ADMINISTRATION

Adults

One tablet containing Montelukast 10mg plus Levocetirizine 5mg once daily. Or as prescribed by the physician.

Elderly

Dosages in the elderly should be adjusted in accordance with their renal function (see Dosage and Administration – Patients with Renal Impairment).

Patients with Renal Impairment

In adults and children 12 years of age and older with:
Mild renal impairment (CrCl 50-80 mL/min): One tablet containing Montelukast 10mg plus Levocetirizine 2.5mg once daily.
Moderate renal impairment (CrCl 30-50 mL/min): One tablet containing Montelukast 10mg plus Levocetirizine 2.5mg once daily, every other day.

Patients with Hepatic Disease

No dosage adjustment is needed in patients solely with mild to moderate hepatic impairment. Usage is not recommended in patients with severe hepatic impairment.

Children and Adolescent

Children aged 15 years above: One tablet containing 10mg Montelukast and Levocetirizine 5mg once daily. Or as prescribed by the physician.

PHARMACODYNAMICS

Montelukast

The cysteinyl leukotrienes (LTC4, LTD4, LTE4) 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 (CysLT1) 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 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.
Montelukast is an orally active compound that binds with high affinity and selectivity to the CysLT1 receptor. Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity.

Levocetirizine

Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H1- receptors.
Binding studies revealed that levocetirizine has high affinity for human H1-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 H1-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.

PHARMACOKINETICS

Montelukast

Absorption

Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (Cmax) is achieved 3 hours (Tmax) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and Cmax are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10 mg film-coated tablet was administered without regard to the timing of food ingestion.
For the 5 mg chewable tablet, the Cmax is achieved in 2 hours after administration in adults in the fasted state. The mean 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 montelukast averages 8-11 liters. Studies in rats with radiolabelled montelukast indicate minimal distribution across the blood-brain barrier. 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 of montelukast are undetectable at steady state in adults and children.
Cytochrome P450 2C8 is the major enzyme in the metabolism of montelukast. Additionally CYP 3A4 and 2C9 may have a minor contribution, although itraconazole, an inhibitor of CYP 3A4, 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 P450 3A4, 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 fecal 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.

Levocetirizine

The pharmacokinetics of levocetirizine are linear with dose- and time-independent with low inter-subject 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 hour 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 o.d. 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. In rats and dogs, the highest tissue levels are found in liver and kidneys, the lowest in the CNS compartment.
In humans, 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 CYP 3A4 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 feces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Montelukast

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 beta-agonist should be used. Patients should seek their doctor's advice as soon as possible if they need more inhalations of short-acting beta-agonists than usual.
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.
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 is often treated with systemic corticosteroid therapy. These cases have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been established, physicians 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.
Treatment with montelukast does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory drugs.

Levocetirizine

Precaution is recommended with concurrent intake of alcohol.
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.
Caution should be taken in patients with epilepsy and patients at risk of convulsion as levocetirizine may cause seizure aggravation.
Response to allergy skin tests are inhibited by antihistamines and a wash-out period (of 3 days) is required before performing them.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.
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.

DRUG INTERACTIONS

Montelukast

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interaction studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, prednisolone, oral contraceptives (norethindrone 1 mg/ethinyl estradiol 35 mcg), terfenadine, digoxin and warfarin.
The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since montelukast is metabolised by CYP 3A4, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, such as phenytoin, phenobarbital and rifampicin.
Although additional specific interaction studies were not performed, montelukast was used concomitantly with a wide range of commonly prescribed drugs in clinical studies without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants.
In vitro studies have shown that montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicinal products primarily 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 (e.g., 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, and 3A4. In a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 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 CYP 2C8, but the physician should 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 no significant increase in the systemic exposure of montelukast.

Levocetirizine

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). A small decrease in the clearance of cetirizine (16%) was observed in a multiple dose study with theophylline (400 mg once a day); while the disposition of theophylline was not altered by concomitant cetirizine administration.
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.
The extent of absorption of levocetirizine is not reduced with food, although the rate of absorption is decreased.
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.

ADVERSE EFFECT

There is no data available on undesirable effects of this combination. However, side effects have been reported with individual molecules.

Montelukast

Montelukast has been evaluated in clinical studies as follows:

- 10 mg film-coated tablets in approximately 4,000 adult and adolescent asthmatic patients 15 years of age and older.
- 10 mg film-coated tablets in approximately 400 adult and adolescent asthmatic patients with seasonal allergic rhinitis 15 years of age and older.

The following drug-related adverse reactions in clinical studies were reported commonly (≥1/100 to <1/10) in asthmatic patients treated 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)
Nervous system disorders	headache
Gastrointestinal disorders	abdominal pain

Tabulated list of Adverse Reactions
Adverse reactions reported in post-marketing use are listed by System Organ Class and specific Adverse Reactions in the table below. Frequency Categories were estimated based on relevant clinical trials.

System Organ Class	Adverse Reactions	Frequency Category*
Infections and infestations	upper respiratory infection†	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
	thrombocytopenia	Very Rare
Immune system disorders	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, tic	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality), obsessive-compulsive symptoms, dysphemia	Very Rare
Nervous system disorders	dizziness, drowsiness, paresthesia/hypoesthesia, seizure	Uncommon
Cardiac disorders	palpitations	Rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS)	Very Rare
	pulmonary eosinophilia	Very Rare
Gastrointestinal disorders	diarrhea‡, 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
	angioedema	Rare
	erythema nodosum, erythema multiforme	Very Rare
Musculoskeletal and connective tissue disorders	arthralgia, myalgia including muscle cramps	Uncommon
Renal and urinary disorders	enuresis in children	Uncommon
General disorders and administration site conditions	pyrexia‡	Common
	asthenia/fatigue, malaise, edema	Uncommon

*Frequency Category: Defined for each Adverse Reaction by the incidence reported in the clinical trials data base: Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), 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

Levocetirizine
Clinical studies
Adults and adolescents above 12 years of age
In therapeutic studies in women and men aged 12 to 71 years, 15.1% of the patients in the levocetirizine 5 mg group had at least one adverse drug reaction compared to 11.3% in the placebo group. 91.6 % of these adverse drug reactions were mild to moderate.
In therapeutic trials, the dropout rate due to adverse events was 1.0% (9/935) with levocetirizine 5 mg and 1.8% (14/771) with placebo.
Clinical therapeutic trials with levocetirizine included 935 subjects exposed to the medicinal product at the recommended dose of 5 mg daily. From this pooling, following incidence of adverse drug reactions were reported at rates of 1% or greater (common: ≥1/100 to <1/10) under levocetirizine 5 mg or placebo:

Preferred Term (WHOART)	Placebo (n = 771)	Levocetirizine 5 mg (n = 935)
Headache	25 (3.2%)	24 (2.6%)
Somnolence	11 (1.4%)	49 (5.2%)
Dry mouth	12 (1.6%)	24 (2.6%)
Fatigue	9 (1.2%)	23 (2.5%)

Further uncommon incidences of adverse reactions (uncommon ≥1/1,000 to <1/100) like asthenia or abdominal pain were observed.
The incidence of sedating adverse drug reactions such as somnolence, fatigue, and asthenia was altogether more common (8.1%) under levocetirizine 5 mg than under placebo (3.1%).

Post-marketing experience
Adverse reactions from post-marketing experience are per System Organ Class and per frequency. The frequency is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

- *Immune system disorders*
  Not known: hypersensitivity including anaphylaxis
- *Metabolism and nutrition disorders*
  Not known: increased appetite
- *Psychiatric disorders*
  Not known: aggression, agitation, hallucination, depression, insomnia, suicidal ideation, nightmare
- *Nervous system disorders*
  Not known: convulsion, paresthesia, dizziness, syncope, tremor, dysgeusia
- *Ear and labyrinth disorders*
  Not known: vertigo
- *Eye disorders*
  Not known: visual disturbances, blurred vision, occulogyration
- *Cardiac disorders*
  Not known: palpitations, tachycardia
- *Respiratory, thoracic and mediastinal disorders*
  Not known:dyspnea
- *Gastrointestinal disorders*
  Not known: nausea, vomiting, diarrhea
- *Hepatobiliary disorders*
  Not known: hepatitis
- *Renal and urinary disorders*
  Not known: dysuria, urinary retention
- *Skin and subcutaneous tissue disorders*
  Not known: angioneurotic edema, fixed drug eruption, pruritus, rash, urticaria
- *Musculoskeletal, connective tissues, and bone disorders*
  Not known: myalgia, arthralgia
- *General disorders and administration site conditions*
  Not known: edema
- *Investigations*
  Not known: increased weight, abnormal liver function tests

Description of selected adverse reactions
After levocetirizine discontinuation, pruritus has been reported.

USE IN PREGNANCY AND LACTATION
Pregnancy
Montelukast
Animal studies do not indicate harmful effects with respect to effects on pregnancy or embyonic/fetal development.
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.
Montelukast may be used during pregnancy only if it is considered to be clearly essential.

Levocetirizine
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of levocetirizine in pregnant women. However, for cetirizine, the racemate of levocetirizine, a large amount of data (more than 1000 pregnancy outcomes) on pregnant women indicate no malformative or fetal/neonatal toxicity. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embyonic/fetal development, parturition or postnatal development.
The use of levocetirizine may be considered during pregnancy, if necessary.

Breast-feeding
Montelukast
Studies in rats have shown that montelukast is excreted in milk. It is unknown whether montelukast/metabolites are excreted in human milk.
Montelukast may be used in breast-feeding only if it is considered to be clearly essential.

Levocetirizine
Cetirizine, the racemate of levocetirizine, has been shown to be excreted in human. Therefore, the excretion of levocetirizine in human milk is likely. Adverse reactions associated with levocetirizine may be observed in breastfed infants. Therefore, caution should be exercised when prescribing levocetirizine to lactating women.

OVERDOSE AND TREATMENT
There is no data reported on the overdosage of this combination. However, overdosage has been reported with individual molecules.

Montelukast
In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult patients for 22 weeks and in short term studies, up to 900 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. These include reports in adults and children with a dose as high as 1,000 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 pediatric patients. There were no adverse experiences in the majority of overdose reports.

Symptoms of overdose
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
No specific information is available on the treatment of overdose with montelukast. It is not known whether montelukast is dialyzable by peritoneal- or hemodialysis.

Levocetirizine
Symptoms
Symptoms of overdose may include drowsiness in adults. In children, agitation and restlessness may initially occur, followed by drowsiness.

Management of overdoses
There is no known specific antidote to levocetirizine.
Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage may be considered shortly after ingestion of the drug. Levocetirizine is not effectively removed by hemodialysis.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA : www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORE AT TEMPERATURES NOT EXCEEDING 30°C. PROTECT FROM LIGHT.

AVAILABILITY

Montelukast sodium + Levocetirizine hydrochloride (Co-Altria®) 10mg/5mg Tablet in Alu/Alu Blister Pack x 10's, (Box of 30's).

Co-Altria® is a registered trademark of Ajanta Pharma Philippines, Inc.

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