MONTELUKAST / LEVOCETIRIZINE HCl

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CO-ALTRIA PED®

5mg/2.5mg Chewable Tablet

5mg/5mg Chewable Tablet

LEUKOTRIENE RECEPTOR ANTAGONIST/ ANTIHISTAMINE

FORMULATION

Each chewable tablet contains:
Montelukast (as sodium), USP..... 5mg
Levocetirizine hydrochloride, USP..... 2.5mg
Each chewable tablet contains:
Montelukast (as sodium), USP.....5mg
Levocetirizine hydrochloride, USP 5mg

DESCRIPTION

5mg/2.5mg Chewable Tablet: Light pink to pink coloured, with slightly mottled appearance, circular, biconvex, uncoated tablet, plain on both sides.
5mg/5mg Chewable Tablet: Light yellow to yellow coloured, circular, biconvex, uncoated tablet, plain on both sides.

INDICATIONS

MONTELUKAST PLUS LEVOCETIRIZINE is indicated for relief of symptoms associated with seasonal and perennial allergic rhinitis.

CONTRAINDICATIONS

It is contraindicated in patients with known hypersensitivity to Montelukast, Levocetirizine, to other piperazine derivatives, or to any of the excipients. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Also contradicted in patients with severe renal impairment at less than 10 mL/min creatinine clearance.

DOSAGE AND ADMINISTRATION

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 Adolescents

Children aged 6-14: One chewable tablet containing 5mg Montelukast and 2.5mg Levocetirizine or 5mg Montelukast and 5mg Levocetirizine 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 receptor occupancy of 90% at 4 hours and 57% at 24 hours.
The onset of action of Levocetirizine 5 mg in controlling pollen-induced symptoms has been observed at 1 hour post drug 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.
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.
Pharmacokinetic/pharmacodynamic relationship: 5 mg Levocetirizine provide a similar pattern of inhibition of histamine-induced wheal and flare than 10 mg cetirizine. As for cetirizine, the action on histamine-induced skin reactions was out of phase with the plasma concentrations. ECGs did not show relevant effects of Levocetirizine on QT interval.

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 three 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 two 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 litres. Studies in rats with radio labelled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radio labelled material at 24 hours post-dose were minimal in all other tissues.
Metabolism: Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of Montelukast are undetectable at steady state in adults and pediatric patients.
Elimination: 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 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.
In several studies, the mean plasma half-life of Montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of Montelukast is nearly linear for oral doses up to 50 mg. During once-daily dosing with 10 mg Montelukast, there is little accumulation of the parent drug in plasma (14%).

Levocetirizine

The pharmacokinetics of Levocetirizine is 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. Peak plasma concentrations are achieved 0.9 g h after dosing. Steady state is achieved after two days. Peak concentrations are typically 270ng/ml and 308ng/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. 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 mean apparent total body clearance 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 WARNING AND PRECAUTIONS FOR USE

Montelukast

Eosinophilic Conditions: In rare cases, patients on therapy with 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 events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between Montelukast and these underlying conditions has not been established.
Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking Montelukast.
Neuropsychiatric events have been reported in adults, adolescents, and children.

Levocetirizine

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.
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. Avoid concurrent use of alcohol with Levocetirizine.

DRUG INTERATIONS

Montelukast

In drug-interaction studies, the recommended clinical dose of Montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisolone, oral contraceptives (norethindrone 1 mg/ethinyl estradiol 35 mcg), terfenadine, digoxin, and warfarin. 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. Phenobarbital, which induces hepatic metabolism, decreased the AUC of Montelukast approximately 40% following a single 10 mg dose of Montelukast.
No dosage adjustment for Montelukast is recommended. It is reasonable to employ appropriate clinical monitoring when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are co-administered with Montelukast.

Levocetirizine

In vitro data indicate that Levocetirizine is unlikely to produce pharmacokinetic interactions through inhibition or induction of liver drug-metabolizing enzymes. No in vivo drug-drug interaction studies have been performed with Levocetirizine. Drug interaction studies have been performed with racemic cetirizine. Pharmacokinetic interaction studies performed with racemic cetirizine demonstrated that cetirizine did not interact with antipyrine, pseudoephedrine, erythromycin, azithromycin, ketoconazole and cimetidine. There was a small decrease (~16%) in the clearance of cetirizine caused by a 400 mg dose of theophylline. It is possible that higher theophylline doses could have a greater effect. The extent of absorption of Levocetirizine is not reduced with food, although the rate of absorption is decreased.
Ritonavir increased the plasma AUC of cetirizine by about 42% accompanied by an increase in half-life (53%) and a decrease in clearance (29%) of cetirizine. The disposition of ritonavir was not altered by concomitant cetirizine administration.
In sensitive patients the simultaneous administration of cetirizine or Levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, although it has been shown that the racemate cetirizine does not potentiate the effect of alcohol.
Renal Impairment: Levocetirizine is known to be substantially excreted by the kidneys and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Dosage adjustment may be

required in patients with impaired renal function. Hence this combination should be used with caution in such patients.
Hepatic Impairment: As Levocetirizine is mainly excreted unchanged by the kidneys, it is unlikely that the clearance of Levocetirizine is significantly decreased in patients with solely hepatic impairment. But Montelukast is mainly excreted through bile; caution is to be exercised while prescribing this combination in patients with impaired hepatic function.

ADVERSE EFFECTS

Montelukast

Montelukast has been evaluated for clinical studies in approximately 4,000 adult and adolescent patients 15 years of age and older for 10 mg and approximately 1,750 paediatric patients and adolescents 6 to 14 years of age for 5 mg.
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: Adult and Adolescent Patients 15 years and older (two 12-week studies; n=795) (A), Paediatric Patients 6 to 14 years old (one 8-week study; n=201) (two 56-week studies; n=615) (P), Nervous system disorders: (A) headache, (P) headache, Gastrointestinal disorders: (A) abdominal pain
Tabulated list of Adverse Reactions
Adverse reactions reported in post-marketing use are listed, by System Organ Class and specific Adverse Experience Term, in the table below. Frequency Categories were estimated based on relevant clinical trials.

System Organ Class	Adverse Experience Term	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[a])	Uncommon
	disturbance in attention, memory impairment, tic	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality), Dysphemia	Very Rare
Nervous system disorders	dizziness, drowsiness paraesthesia/hypoesthesia, seizure	Uncommon
Cardiac disorders	palpitations	Rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS) (see section 4.4)	Very Rare
	pulmonary eosinophilia	Very Rare
Gastrointestinal disorders	diarrhoea‡, 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
	angiooedema	Rare
	erythema nodosum, erythema multiforme	Very Rare
Musculoskeletal, connective tissue and bone 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, oedema	Uncommon

*Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), 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

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 drug at the recommended dose of 5 mg daily. From this data, the following adverse drug reactions were reported at rates of 1 % or greater during treatment with Levocetirizine 5 mg (L) or placebo (P); Headache: L (2.6%), P (3.2%). Somnolence: L (5.2%), P (1.4%). Dry Mouth: L (2.6%), P (1.6%). Fatigue: L (2.5%), P (1.2%).
Pediatric population: In two placebo-controlled studies in pediatric patients aged 6-11 months and aged 1 year to less than 6 years, 159 subjects were exposed to levocetirizine at the dose of 1.25 mg daily for 2 weeks and 1.25 mg twice daily respectively. The following incidence of adverse drug reactions was reported at rates of 1% or greater under levocetirizine or placebo (L) or placebo (P); Diarrhoea: L (1.9%), Vomiting: L (0.6%), P (1.2%). Constipation: L (1.3%), Somnolence: L (1.9%), P (2.4%), Sleep disorder: L (1.3%).
In children aged 6-12 years double blind placebo controlled studies were performed where 243 children were exposed to 5 mg levocetirizine daily for variable periods ranging from less than 1 week to 13 weeks. The following incidence of adverse drug reactions was reported at rates of 1% or greater under levocetirizine or placebo. (L) or placebo (P); Headache: L (0.8%), P (2.1%), Somnolence: L (2.9%), P (0.4%).
List of Adverse Reactions: 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, paraesthesia, dizziness, syncope, tremor, dysgeusia
• *Ear and labyrinth disorders*
Not known: vertigo
• *Eyes disorders*
Not known: visual disturbances, blurred vision, oculogyration
• *Cardiac disorders*
Not known: palpitations, tachycardia
• *Respiratory, thoracic and mediastinal disorders*
Not known: dyspnoea
• *Gastrointestinal disorders*
Not known: nausea, vomiting, diarrhoea
• *Hepatobiliary disorders*
Not known: hepatitis
• *Renal and urinary disorders*
Not known: dysuria, urinary retention
• *Skin and subcutaneous tissue disorders*
Not known: angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria
• *Musculoskeletal, connective tissues, and bone disorders*
Not known: myalgia, arthralgia
• *General disorders and administration site conditions*
Not known: oedema
• *Investigations*
Not known: weight increased, abnormal liver function tests
After levocetirizine discontinuation, pruritus has been reported.

OVERDOSE AND TREATMENT

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

Montelukast

There have been reports of acute overdosage in post-marketing experience and clinical studies with Montelukast. These include reports in adults and children with a dose as high as 1000 mg. 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 overdosage reports. 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. It is not known whether Montelukast is removed by peritoneal dialysis or hemodialysis.

Levocetirizine

Symptoms of overdose may include drowsiness in adults. There is no known specific antidote to Levocetirizine. Should overdose occur, symptomatic or supportive treatment is recommended. Levocetirizine is not effectively removed by dialysis and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested.

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.

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

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

CO-ALTRIA PED® is a registered trademark of Ajanta Pharma Philippines, Inc.

AVAILABILITY
Montelukast sodium + Levocetirizine hydrochloride (CO-ALTRIA PED®) 5mg/2.5mg Chewable Tablet x Alu-Alu blister pack of 10's, box of 30 chewable tablets
Montelukast sodium + Levocetirizine hydrochloride (CO-ALTRIA PED®) 5mg/5mg Chewable Tablet x Alu-Alu blister pack of 10's, box of 30 chewable tablets

REGISTRATION NUMBER
5mg/2.5mg Chewable Tablet: DRP-11748
5mg/5mg Chewable Tablet: DRP-11749

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