Meftan® Plus (Tablets)

31300

Ref. No: B2131300/24.03

Montelukast sodium / Leukotriene receptor antagonist
Levocetirizine DiHCL / Antihistaminic

MEFTAN®PLUS 10/5 TABLETS (FILM COATED)
MEFTAN®PLUS DT 4/2.5 TABLETS (DISPERSIBLE)

PRESENTATION:
Meftan® Plus 10/5 mg Film coated Tablets: Yellow, circular, biconvex tablet 'C' on one side and plain on other the side. Each film coated tablet contains: Montelukast, Levocetirizine, Lactose, Tartrazine yellow water soluble and other excipients.
Meftan® Plus DT 4/2.5 mg Dispersible Tablets: White to yellowish white circular, biconvex tablet 'C' on one side and plain on other the side. Each dispersible tablet contains: Montelukast, Levocetirizine, Lactose, and other excipients.

CLINICAL PHARMACOLOGY:
Levocetirizine
Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H1-receptors. 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.
Montelukast
The cysteinyl leukotrienes (LTC4, LTD4, LTE4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils which bind to cysteinyl leukotriene (CysLT) receptors found in the human airway (including airway smooth muscle cells and airway macrophages) and on pro-inflammatory cells (including eosinophils and certain myeloid stem cells). In asthma, leukotriene-mediated effects include bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

PHARMACOKINETICS:
Levocetirizine
Absorption
Levocetirizine is rapidly and extensively absorbed following oral administration. Peak plasma concentrations are achieved 0.9h 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 human, 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 negligible. Metabolic pathways include aromatic oxidation, N- and O- Dealkylation and taurine conjugation
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 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.

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.
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 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. 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 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.

USES:
Meftan® Plus is indicated for relief of symptoms of allergic rhinitis in age of 15 years and above, as prophylaxis in seasonal allergic rhinitis, urticaria in adults and treatment of comorbid asthma.

DOSAGE AND ADMINISTRATION:
Meftan Plus
Adult (age above 15 years)
One tablet daily OR as per physician direction.
Meftan plus DT
For children (2 to 5 years)
One tablet daily OR as per physician direction.
Directions for use: Place the tablet in a teaspoon. Add little water. The tablet will disperse in less than 60 seconds. Give the spoonful to the child.
Not recommended for children below 2 years.

Meftan® Plus (Tablets)

CONTRA-INDICATIONS
- Hypersensitivity to the active substances or to any of the excipients.
- It is contraindicated in patients with renal impairment as less than 10mL/min creatinine clearance
· Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

ADVERSE EFFECTS:
Diarrhoea, vomiting, constipation, somnolence, sleep disorder, fatigue, upper respiratory infection, Headache and abdominal pain, increased bleeding tendency, thrombocytopenia, hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration, 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, hallucinations, disorientation, suicidal thinking and behaviour (suicidality), obsessive-compulsive symptoms, dysphemia.

OVERDOSAGE:
Symptoms
Symptoms of overdose may include drowsiness in adults. In children, agitation and restlessness may initially occur, followed by drowsiness. The most frequently occurring symptoms included abdominal pain, somnolence, thirst, headache, vomiting and psychomotor hyperactivity.
Management of overdoses
There is no known specific antidote to Levocetirizine. No specific information is available on the treatment of overdose with Montelukast. Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage should be considered shortly after ingestion of the drug. Levocetirizine is not effectively removed by haemodialysis. It is not known whether Montelukast is dialysable by peritoneal-or haemo-dialysis.

DRUG INTERACTIONS
Levocetirizine
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 (400mg once a day). 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.
Montelukast
Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. The recommended clinical dose of Montelukast did not have clinically important effects on the pharmacokinetics of the following medicinal products: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/ norethindrone 35/1), terfenadine, digoxin and warfarin. 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 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.)

SPECIAL WARNINGS AND PRECAUTIONS:
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.
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 β-agonist should be used. Patients should seek their doctor's advice as soon as possible if they need more inhalations of short-acting β-agonists than usual. Montelukast should not be substituted abruptly for inhaled or oral corticosteroids.

PREGNANCY AND BREASTFEEDING:
Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development therefore the use of Meftan® Plus may be considered during pregnancy, if necessary.
Breastfeeding
Adverse reactions associated with levocetirizine may be observed in breastfed infants. Montelukast may be used in breast-feeding only if it is considered to be clearly essential. Therefore, caution should be exercised when prescribing Meftan® Plus to lactating women.

PHARMACEUTICAL PRECAUTIONS:
Store in a dry place below 30˚C. Protect from light. Keep all medicines out of the reach of children.

LEGAL CATEGORY:
Prescription Only Medicine (POM)

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COSMOS
Cosmos Limited,
Rangwe Rd; Off Lunga Lunga Rd,
Nairobi, Kenya