403304/04

Clarinase®

24hr Extended Release Tablet

Brand of Loratadine and Pseudoephedrine sulfate

Extended-Release, Non-sedating Antihistamine/Decongestant Tablets

DESCRIPTION:

Each Clarinase®24 Hr Tablets contains 10 mg loratadine in the tablet coating and 240 mg pseudoephedrine sulfate in the tablet core. The loratadine component is released immediately, whereas the pseudoephedrine component is released slowly from the core allowing for once daily administration. Excipients: Hydroxypropyl Methylcellulose, Ethylcellulose, Calcium Hydrogen Phosphate, Polyvidone, Silicon Dioxide, Magnesium Stearate, Hydroxypropyl Methylcellulose, Polyethylene Glycol, White Color Dispersion and Macrogol 400.

Appearance: White to off-white, oval, biconvex coated tablet.

ACTIONS:

Loratadine is a potent long-acting antihistamine with selective peripheral H1-receptor antagonistic activity.

Pseudoephedrine sulfate, one of the naturally occurring alkaloids of Ephedra and an orally administered vasoconstrictor, produces a gradual but sustained decongestant effect facilitating shrinkage of congested mucosa in upper respiratory areas. The mucous membrane of the respiratory tract is decongested through the action on the sympathetic nerves.

The combination of loratadine and pseudoephedrine sulfate controls histamine mediated symptoms and relieves the nasal congestion associated with allergic rhinitis and the common cold.

PHARMACODYNAMIC PROPERTIES:

During studies of its effects on the CNS, loratadine has exhibited no depressant activity and no acute anticholinergic activity.

Loratadine has exhibited a very low affinity for membrane receptors from the cerebral cortex and does not readily penetrate into the CNS. Whole body autoradiographic studies in rats and monkeys, radiolabeled tissue distribution studies in mice and rats, and in vivo radioligand studies in mice have shown that neither loratadine nor its metabolites readily cross the blood-brain barrier.

Radioligand binding studies with guinea pig pulmonary and brain H1-receptors indicate that there was preferential binding to peripheral versus central nervous system H1-receptors.

The sedation profile of loratadine, 10 mg daily, is comparable to that of placebo and, during long term treatment, there were no clinically significant changes in vital signs, laboratory test values, physical examinations or electrocardiograms. In studies with loratadine tablets at doses two to four times higher than the recommended dose of 10 mg, a dose-related increase in the incidence of somnolence was observed.

Loratadine has no significant H2-receptor activity, does not inhibit norepinephrine uptake and has practically no influence on cardiovascular function or on intrinsic cardiac pacemaker activity. In a study in which loratadine tablets were administered at four times the clinical dose for 90 days, no clinically significant increase in the QTc was seen on ECGs.

Pseudoephedrine acts directly on both α- and to a lesser degree, β-adrenergic receptors. It is believed that α-adrenergic effects result from the inhibition of the production of cyclic adenosine-3′, 5′-monophosphate (AMP) by inhibition of the enzyme adenyl cyclase, whereas β-adrenergic effects result from stimulation of adenyl cyclase activity. Like ephedrine, pseudoephedrine also has an indirect effect by releasing norepinephrine from its storage sites.

Pseudoephedrine acts directly on α-adrenergic receptors in the mucosa of respiratory tract producing vasoconstriction which results in shrinkage of swollen nasal mucous membranes, reduction of tissue hyperemia, edema and nasal congestion, and in an increase in nasal airway patency. Drainage of sinus secretions is increased and obstructed eustachian ostia may be opened.

Pseudoephedrine may relax bronchial smooth muscle by stimulation of β2-adrenergic receptors; however, substantial bronchodilation has not been demonstrated consistently following oral administration of the drug.

Oral administration of usual doses of pseudoephedrine to normotensive patients usually produces negligible effect on blood pressure. Pseudoephedrine may increase the irritability of the heart muscle and may alter the rhythmic function of the ventricles, especially in large doses or after administration to patients such as those with cardiac disease who are hypersensitive to the myocardial effects of sympathomimetic drugs. Tachycardia, palpitation, and/or multifocal premature ventricular contractions may occur.

Pseudoephedrine may cause mild CNS stimulation, especially in patients who are sensitive to the effects of sympathomimetic drugs.

PHARMACOKINETICS:

Loratadine - After oral administration, loratadine is rapidly and well absorbed and undergoes an extensive first pass metabolism. In normal subjects, plasma distribution half-lives of loratadine and its active metabolite are approximately 1 and 2 hours, respectively. Initial data in normal subjects demonstrated a mean elimination half-life of 12.4 hours for loratadine and 19.6 hours for the active metabolite.

Subsequent data in normal adult subjects demonstrated mean elimination half-lives of 8.4 hours (range=3 to 20 hours) for loratadine and 28 hours (range=8.8 to 92 hours) for the major active metabolite. In nearly all patients, exposure (AUC) to the metabolite was greater than exposure to the parent compound.

Loratadine is highly bound (97% to 99%) and its active metabolite moderately bound (73% to 76%) to plasma proteins.

The bioavailability parameters of loratadine and of the active metabolite are dose proportional.

Approximately 40% of the dose is excreted in the urine and 42% in the feces over a 10-day period and that, mainly in the form of conjugated metabolites.

Approximately 27% of the dose is eliminated in the urine during the first 24 hours. Traces of unchanged loratadine and of its active metabolite were found in the urine.

The pharmacokinetic profile of loratadine and its metabolites is comparable in healthy adult volunteers and in healthy geriatric volunteers.

In patients with chronic renal impairment, both the AUCs and peak plasma levels (Cmax) increased for loratadine and its metabolite as compared to the AUCs and peak plasma levels (Cmax) of patients with normal renal function. The mean elimination half-lives of loratadine and its metabolite were not significantly different from that observed in normal subjects. Hemodialysis does not have an effect on the pharmacokinetics of loratadine or its active metabolite in subjects with chronic renal impairment.

In patients with chronic alcoholic liver disease, the AUC and peak plasma levels (Cmax) of loratadine were double while the pharmacokinetic profile of the active metabolite was not significantly changed from that in patients with normal liver function. The elimination half-lives of loratadine and its metabolite were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

Loratadine and its active metabolite are excreted in the breast milk of lactating women. Forty-eight hours after dosing, only 0.029% of the loratadine dose is detected in the milk as unchanged loratadine and its active metabolite.

Pseudoephedrine: Absorption - After oral administration of 60 mg of pseudoephedrine hydrochloride as tablets or oral solution, nasal decongestion occurs within 30 minutes and persists for 4-6 hours. Nasal decongestion may persist for 8 hours following oral administration of 60 mg and up to 12 hours following 120 mg of the drug in extended-release preparations.

Distribution - Although specific information is lacking, pseudoephedrine is presumed to cross the placenta and to enter CSF. The drug may also be distributed into milk.

Elimination - Pseudoephedrine is incompletely metabilized in the liver by N-demethylation to an inactive metabolite. The drug and its metabolite are excreted in urine; 55-75% of a dose is excreted unchanged. The rate of urinary excretion of pseudoephedrine is accelerated when urine is acidified to a pH of about 5 by prior administration of ammonium chloride. When the urine is alkalinized to a pH of about 8 by prior administration of sodium bicarbonate, some of the drug is reabsorbed in the kidney tubule and the rate of urinary excretion is slowed.

INDICATIONS AND USAGE:

CLARINASE 24Hr Tablets are indicated for the relief of symptoms associated with allergic rhinitis and the common cold, including nasal congestion, sneezing, rhinorrhea, pruritus and lacrimation.

CLARINASE 24Hr Tablets are recommended when both the antihistaminic properties of loratadine and the decongestant effect of pseudoephedrine sulfate are desired.

DOSAGE AND ADMINISTRATION:

Adults and Children 12 years of age and over: One CLARINASE 24Hr Tablets once daily. CLARINASE 24Hr Tablets may be taken without regard to meal time.

Patients who have a history of difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis should not use this product (see PRECAUTIONS and ADVERSE REACTIONS).

DRUG INTERACTIONS:

When administered concomitantly with alcohol, loratadine has no potentiating effect as measured by psychomotor performance studies.

Increase in plasma concentrations of loratadine has been reported after concomitant use with ketoconazole, erythromycin or cimetidine in controlled clinical trials, but without clinically significant changes (including electrocardiographic). Other drugs known to inhibit hepatic metabolism should be coadministered with caution until definitive interaction studies can be completed.

When sympathomimetic drugs are given to patients receiving monoamine oxidase (MAO) inhibitors, hypertensive reactions, including hypertensive crisis may occur. The antihypertensive effects of methyldopa, mecamylamine, reserpine and veratrum alkaloids may be reduced by sympathomimetics. Beta-adrenergic blocking agents also may interact with sympathomimetics. Increased ectopic pacemaker activity can occur when pseudoephedrine sulfate is used concomitantly with digitalis. Antacids increase the rate of pseudoephedrine sulfate absorption; kaolin decreases it.

Drug/Laboratory Test Interactions: Antihistamines should be discontinued approximately 48 hours prior to skin testing procedures since these drugs may prevent or diminish otherwise positive reactions to dermal reactivity indicators.

The in vitro addition of pseudoephedrine to sera containing the cardiac soenzyme MB of serum creatine phosphokinase progressively inhibits the activity of the enzyme. The inhibition becomes complete over six hours.

ADVERSE REACTIONS:

During controlled clinical studies with the recommended dosage, the incidence of adverse effects associated with CLARINASE 24Hr Tablets was similar to that of placebo, with the exception of insomnia and dry mouth. Other reported adverse reactions associated with both CLARINASE 24Hr Tablets and placebo included headache and somnolence.

From post-marketing experience, isolated cases of acute generalized exanthematous pustulosis (AGEP), a form of severe skin reaction, have been reported with pseudoephedrine-containing products. During the marketing of loratadine, the following adverse effects have been reported rarely: alopecia, anaphylaxis (including angioedema), abnormal hepatic function, dizziness, and convulsion.

There have been rare postmarketing reports of mechanical upper gastrointestinal tract obstruction in patients taking CLARINASE 24Hr Tablets. In most of these cases, patients have had a history of difficulty in swallowing tablets, or have had known upper gastrointestinal narrowing or abnormal esophageal peristalsis.

CONTRAINDICATIONS:

CLARINASE 24Hr Tablets are contraindicated in those who have shown sensitivity or idiosyncrasy to their components or to adrenergic agents. CLARINASE 24Hr Tablets also are contraindicated in patients receiving MAO inhibitor therapy or within two weeks of discontinuing such treatment and in patients with narrow angle glaucoma, urinary retention, severe hypertension, severe coronary artery disease and hyperthyroidism.

PRECAUTIONS:

Sympathomimetic amines should be used judiciously in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, or prostatic hypertrophy.

Central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension may be produced by sympathomimetic amines.

Acute generalized exanthematous pustulosis (AGEP), a form of severe skin reaction, may occur with pseudoephedrine-containing products in isolated cases. If signs and symptoms such as fever, erythema, or small (generalized) pustules are observed, patients should discontinue to use the drug and consult their physician.

Patients with hepatic insufficiency should be given a lower initial dose (one tablet every other day) because of reduced clearance of loratadine.

Patients who have a history of difficulty in swallowing tablets or who have known gastrointestinal narrowing or abnormal esophageal peristalsis should not use this product.

Drug Abuse and Dependence: No data are available to indicate that abuse or dependency occurs with loratadine.

Like other CNS stimulants, pseudoephedrine sulfate has a potential for abuse, and increased doses may ultimately produce toxicity. Depression may follow rapid withdrawal.

PEDIATRIC USAGE:

Safety and efficacy of CLARINASE 24Hr Tablets in children youngen than 12 years of age have not yet been established.

USAGE DURING PREGNANCY AND IN NURSING MOTHERS:

Safe use of CLARINASE 24Hr Tablets during pregnancy has not been established. Therefore, the product should be used only if the potential benefit justifies the potential risk to the fetus.

Since loratadine and pseudoephedrine sulfate are excreted in breast milk, a decision should be made whether to discontinue nursing or to discontinue the use of this product.

OVERDOSAGE INFORMATION:

To date, overdosage has not been reported with CLARINASE 24Hr Tablets. In the event of overdosage, general symptomatic and supportive treatment should be started immediately and maintained for as long as necessary.

Manifestations: These may vary from CNS depression (sedation, apnea, diminished mental alertness, cyanosis, coma, cardiovascular collapse) to stimulation (insomnia, hallucination, tremors or convulsions) to death. Other signs and symptoms may be euphoria, excitement, tachycardia, palpitations, thirst, perspiration, nausea, dizziness, tinnitus, ataxia, blurred vision and hypertension or hypotension. Stimulation is particularly likely in children, as are atropine-like signs and symptoms (dry mouth; fixed, dilated pupils; flushing; hyperthermia; and gastrointestinal symptoms).

In large doses sympathomimetics may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscular weakness, tenseness, anxiety, restlessness and insomnia. Some patients present a toxic psychosis with delusions and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsions, coma and respiratory failure.

The Oral LK50 values for loratadine and pseudoephedrine sulfate in combination product were approximately 600 mg/kg in mice and 2000 mg/kg in rats. Cynomolgus monkeys tolerated single doses of up to 240 mg/kg.

Treatment: The patient should be induced to vomit, even if emesis has occurred spontaneously. Pharmacologically-induced vomiting by the administration of ipecac syrup is a preferred method. However, vomiting should not be induced in patients with impaired consciousness. The action of ipecac is facilitated by physical activity and by the administration of 240 to 360 milliliters of water. If emesis does not occur within 15 minutes, the dose of ipecac should be repeated. Precautions against aspiration must be taken, especially in children. Following emesis, adsorption of any drug remaining in the stomach may be attempted by the administration of activated charcoal as a slurry with water. If vomiting is unsuccessful, or contraindicated, gastric lavage should be performed. Physiologic saline solution is the lavage solution of choice, particularly in children. In adults, tap water can be used; however, as much as possible of the amount administered should be removed before the next instillation. Saline cathartics draw water into the bowel by osmosis and therefore may be valuable for their action in rapid dilution of bowel content. Loratadine is not removed by hemodialysis; it is not known if loratadine is removed by peritoneal dialysis. After emergency treatment, the patient should continue to be medically monitored.

Treatment of the signs and symptoms of overdosage is symptomatic and supportive. Stimulants (analeptic agents) should not be used. Vasopressors may be used to treat hypotension. Short-acting barbiturates, diazepam or paraldehyde may be administered to control seizures. Hyperpyrexia, especially in children, may require treatment with tepid water sponge baths or hypothermic blanket. Apnea is treated with ventilatory support.

HOW SUPPLIED:

Blister packs of 10 tablets.

STORAGE:

Store below 30°C.
Protect blister packs from excessive moisture.
Shelf-life information can be found on outer labels of the product.
Keep medicines out of reach of children.

Further information can be obtained from the doctor or the pharmacist.

PRODUCT REGISTRATION HOLDER:

Bayer Co. (Malaysia) Sdn Bhd

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