SUMMARY OF PRODUCT CHARACTERISTICS

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NAME OF THE MEDICINAL PRODUCT

Clarinase Repatabs

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Clarinase Tablets contains 5 mg loratadine in the tablet coating and 120 mg of pseudoephedrine sulfate equally distributed between tablet coating and tablet core.

PHARMACEUTICAL FORM

Extended-Release Tablet

CLINICAL PARTICULARS

Indication(s)

Clarinase Tablets are indicated for the relief of symptoms of allergic rhinitis (and the common cold, if approved locally).

Clarinase Tablets are recommended when both the antihistamine activity of loratadine and the decongestant effect of pseudoephedrine sulfate are desired.

Dosage and method of administration

Method of administration

For oral use.

Dosage regimen

Adults (including geriatric patients):

One Clarinase tablet twice daily (every 12 hours).

Children 12 years of age and over:

One Clarinase tablet twice daily (every 12 hours).

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Contraindications

Clarinase Tablets are contraindicated in patients who are hypersensitive or show idiosyncrasy to this medication, to any of its ingredients, to adrenergic agents, or to other drugs of similar chemical structures.

This product, due to its pseudoephedrine component, is contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen days of stopping such treatment (see section 4.4 Special warnings and precautions for use). It is also contraindicated in patients with severe hypertension and severe coronary artery disease.

Special warnings and precautions for use

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

Central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension may be produced by sympathomimetic amines. The elderly are more likely to have adverse reactions from 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.

Because the doses of this fixed combination product cannot be individually titrated, Clarinase Tablets should generally be avoided in patients with severe hepatic insufficiency.

Patients with severe renal insufficiency should be given a lower initial daily dose (one tablet per day).

Patients should also be advised against the concurrent use of CLARITIN-D 12 HOUR Extended Release Tablets with over-the-counter antihistamines and decongestants.

Patients should be instructed not to break or chew the tablet.

Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been conducted with CLARITIN-D 12 HOUR Extended Release Tablets.

Loratadine

Increase in plasma concentrations of loratadine has been reported with concomitant use with ketoconazole, erythromycin or cimetidine in controlled clinical trials, but without clinically significant changes (including electrocardiographic).

Pseudoephedrine sulfate

Concomitant use of this product with monoamine oxidase (MAO) inhibitors can cause blood pressure increase; this interaction is still possible two weeks after MAO inhibitor therapy.

The antihypertensive effects of drugs influencing the sympathetic system such as methyldopa, mecamylamine, reserpine and veratrum alkaloids may be reduced by sympathomimetics.

Beta-adrenergic blocking agents may also interact with sympathomimetics by reducing their activity.

Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis.

Drug/Laboratory Test Interactions

The *in vitro* addition of pseudoephedrine to sera containing the cardiac isoenzyme MB of serum creatinine phosphokinase progressively inhibits the activity of the enzyme. The inhibition becomes complete over 6 hours.

Fertility, pregnancy and lactation

Pregnancy

Clarinase Tablets should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

There was no evidence of teratogenicity in animal studies (See section 5.3 Preclinical Safety Data). However, the safe use of Clarinase Tablets during pregnancy and lactation has not been established.

Lactation

For nursing mothers, a decision should be made whether to discontinue nursing or discontinue the drug.

Fertility

Women of childbearing potential / Contraception

Safe use of Clarinase Tablets during pregnancy has not been established. Therefore, the product should be used only if the potential benefit justifi es 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.

Effects on ability to drive or use machines

Undesirable effects

The most frequently reported adverse effects in clinical studies (i.e., > 5% incidence) were insomnia, dry mouth, headache, nervousness and somnolence. The reported incidences of somnolence and headache were comparable to placebo.

Palpitations, tachycardia and anorexia, all attributable to pseudoephedrine, were also reported.

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.

The following spontaneous adverse events have been reported rarely during the marketing of loratadine: abnormal hepatic function, alopecia, anaphylaxis including angioedema, dizziness, and convulsion.

Overdose

In the event of overdosage, general symptomatic and supportive treatment should be started immediately and maintained for as long as necessary.

Manifestations

Tachycardia, headache and somnolence have been reported with overdoses of loratadine.

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

Treatment

Treatment of overdosage would reasonably consist of emesis (ipecac syrup), except in patients with impaired consciousness, followed by the administration of activated charcoal to absorb any remaining drug. If vomiting is unsuccessful, or contraindicated, gastric lavage should be performed with normal saline. Saline cathartics may also be of value for rapid dilution of bowel contents.

Loratadine is not eliminated by hemodialysis. It is not known if loratadine is eliminated by peritoneal dialysis.

There is no information to indicate that abuse or dependency occurs with loratadine or the combination of loratadine and pseudoephedrine.

Pseudoephedrine, like other central nervous system stimulants, has been abused. Continued use can result in tolerance and therefore, increase the risk of overdosage.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: pseudoephedrine, combinations

ATC Code: R01BA52

Pharmacodynamic effects

The pharmacodynamic properties of Clarinase Tablets are directly related to that of its components, loratadine, a tricyclic antihistamine with selective peripheral H_1-receptor antagonistic activity, and pseudoephedrine sulfate, an orally active sympathomimetic amine nasal decongestant.

Clinical efficacy and safety

In a study in which loratadine was administered at 40 mg (4 times the clinical dose) for 90 days, no clinically significant increase in the QTc was seen on ECGs.

In a single rising dose study in which doses up to 160 mg (16 times the clinical dose) were studied, loratadine did not cause any clinically significant changes on the QTc interval in the ECGs.

Pharmacokinetic properties

Absorption

Loratadine

After oral administration of loratadine in the conventional tablet formulation, the drug 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.

The AUC and peak plasma levels (C_{max}) of loratadine and its metabolite are about 50% higher in healthy geriatric subjects than in healthy younger adult subjects. This difference is not regarded as clinically important.

The effect of food on the pharmacokinetic profile of loratadine and its metabolites is not regarded as clinically significant.

In patients with chronic renal impairment both the AUC and peak plasma levels (C_{max}) increased for loratadine and its metabolite as compared to the AUCs and C_{max} of patients with normal renal function.

In patients with chronic alcoholic liver disease, the AUC and C_{max} of loratadine were double while the pharmacokinetic profile of the active metabolite was not significantly changed from that in patients with normal liver function.

Pseudoephedrine sulphate

After oral administration, pseudoephedrine sulfate is rapidly and completely absorbed. Onset of action occurs within 30 minutes and a dose of 60 mg has a decongestive action lasting for 4 to 6 hours.

Distribution

Loratadine

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

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 sulphate

The drug may be distributed in breast milk of lactating women.

Metabolism / Biotransformation

Pseudoephedrine sulphate

Pseudoephedrine sulphate undergoes incomplete hepatic metabolism by N-demethylation to an inactive metabolite.

Elimination / Excretion

Loratadine

The mean elimination half-lives found in normal adult subjects were 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for the major active metabolite descarboethoxyloratadine).

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.

In patients with chronic renal impairment, were the mean elimination half-lives of loratadine and its metabolite 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, were the elimination half-lives for loratadine and its metabolite 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

Pseudoephedrine sulphate

Its elimination half-life in humans ranges from 5 to 8 hours. The drug and its metabolite are excreted in urine, 55-75 % of a dose is excreted unchanged.

Linearity / Non-linearity

Loratadine

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

Preclinical safety data

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 lung and brain H_1-receptors indicate that there was preferential binding to peripheral versus central nervous system H_1-receptors.

Toxicity

In acute and repeat dose toxicity studies, the combination of loratadine and pseudoephedrine exhibited low order toxicity. The combination was no more toxic than either component alone and observed effects were generally related to the pseudoephedrine component.

Teratogenicity, Mutagenesis and Carcinogenesis

Based on the available data, loratadine is not teratogenic and poses no mutagenic or carcinogenic risk for patients.

Similarly, pseudoephedrine sulfate is not considered to be teratogenic, mutagenic, or carcinogenic.

The combination of loratadine/pseudoephedrine sulfate was not teratogenic when administered orally in rats up to 150 mg/kg/day (30 times the proposed clinical dose) and in rabbits up to 120 mg/kg/day (24 times the proposed clinical dose) in reproductive toxicity studies.

PHARMACEUTICAL PARTICULARS

List of excipients

Maize starch

Lactose

Magnesium stearate

Povidone

Acacia

Oleic acid

Calcium sulphate

Microcrystalline cellulose

Medicianal soap

Colophony

Sucrose

Talc

Titanium dioxide

Zei

Carnauba wax

White bees wax.

Incompatibilities

None

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Special precautions for storage

Do not store above 25°C.

Nature and contents of container

PVC/Alu blister packs of 14 tablets.

Instructions for use / handling

None

Manufacturer

Schering Plough Labo N.V ,

Industriepark

B-2220

Hest –op-den-Berg

Belgium

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