NAME OF THE MEDICINAL PRODUCT

Loratadine

QUALITATIVE AND QUANTITATIVE COMPOSITION IN TERMS OF THE ACTIVE SUBSTANCE

Loratadine 10mg Tablet, contents per tablet: 10mg loratadine.

Loratadine 5 mg/5mL Syrup, contents per (5mL) teaspoonful: 5mg loratadine.

PHARMACEUTICAL FORM

Tablet

Syrup

Loratadine 10mg tablet: white, round, biconvex, scored tablet. MK logo on one side and LD code on the slotted side, between the slot.

Loratadine 5mg/5mL syrup: transparent, lightly orange solution, with a peach odor.

CLINICAL PARTICULARS

Indications

Loratadine is indicated for the symptomatic relief of allergic conditions including rhinitis and chronic urticaria1 in patients 2 years of age or older.

Dosage and method of administration

Adults and children 6 years of age and over: the recommended dose of Loratadine is one 10 mg tablet or 2 teaspoonfuls (10 mg) of syrup once daily.

Children 2 to 5 years of age: the recommended dose of Loratadine Syrup is 5 mg (1 teaspoonful) once daily.

In adults and children 6 years of age and over with liver failure or renal insufficiency (GFR < 30 mL/min), should be given a lower initial dose: 10 mg (one tablet or two teaspoonfuls) every other day.

In children 2 to 5 years of age with liver failure or renal insufficiency, should be given a lower initial dose: 5 mg (one teaspoonful) every other day.

Contraindications

Loratadine is contraindicated in patients with hypersensitivity to loratadine or any of its ingredients.

Loratadine must not be used during pregnancy or in breast-feeding mothers.

Special warnings and precautions for use

In adults and children 6 years of age and over with liver failure or renal insufficiency (GFR < 30 mL/min), should be given a lower initial dose: 10 mg (one tablet or two teaspoonfuls) every other day.

In children 2 to 5 years of age with liver failure or renal insufficiency, should be given a lower initial dose: 5 mg (one teaspoonful) every other day.

In case of suspected renal insufficiency (e.g. in geriatric patients), renal function should be assessed prior to initiation of loratadine and monitored during therapy. Adjustments in dosage should be made accordingly.

Ocasional reports of convulsions in patients taking antihistamines suggest a need for caution in patients with epilepsy.

Interaction with other medicinal products and other forms of interaction

Loratadine is metabolized by cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Therefore use with other drugs that inhibit or are metabolized by these hepatic enzymes may result in changes in plasma concentrations of either drug and, possibly, adverse effects. Drugs known to inhibit one or other of these enzymes include cimetidine, erythromycin, ketoconazole, quinidine, fluconazole, and fluoxetine.

Antibacterials: data show that erythromycin can inhibit the metabolism of loratadine. However, even when given in large doses loratadine does not appear to cause the cardiac conduction disorders associated with the non-sedating antihistamines astemizole and terfenadine. Similarly, clarithromycin seemed to inhibit the metabolism of loratadine and its active metabolite desloratadine.

Antifungals: ketoconazole also appears to be able to inhibit the metabolism of loratadine and at therapeutic doses, is about 3 times more inhibitory than erythromycin. However, the concentrations of

ketoconazole required are reported to be much higher than those required to inhibit the metabolism of astemizole or terfenadine. Clearance of the active metabolite desloratadine is also reduced.

Gastrointestinals: cimetidine appears to have an inhibitory effect on the metabolism of loratadine and also attenuates the clearance of its active metabolite desloratadine although no clinically significant consequences have been observed.

Pregnancy and lactation

Pregnancy

Loratadine must not be used during pregnancy.

Lactation

Loratadine must not be used in breast-feeding mothers.

Effects on ability to drive or use machines

Reactions to the drug, like dizziness or vertigo, which vary in intensity from individual to individual, can impair the ability to drive or to operate machinery. This applies particularly at the start of treatment, on changing the medication and in combination with alcohol.

Undesirable effects

- AE with an incidence of more than 2% in patients 12 years of age and older: headache, somnolence, fatigue and dry mouth.
- AE with an incidence of ≥2% in patients 6 to 12 years old: nervousness, wheezing, fatigue, hyperkinesia, abdominal pain, conjunctivitis, dysphonia, malaise, upper respiratory tract infection.
- AE that occurred with a frequency of 2 to 3% in patients 2 to 5 years old: diarrhea, epistaxis, pharyngitis, influenza-like symptoms, fatigue, stomatitis, tooth disorder, earache, viral infection, and rash.

Adverse event rates did not appear to differ significantly based on age, sex, or race.

In addition to those adverse events reported above, the following adverse events have been reported in adult and pediatric patients:

Autonomic nervous system: altered lacrimation, altered salivation, flushing, hypoesthesia, impotence, increased sweating, thirst.

Body as a whole: angioneurotic edema, asthenia, back pain, blurred vision, chest pain, earache, eye pain, fever, leg cramps, malaise, rigors, tinnitus, weight gain.

Cardiovascular system: hypertension, hypotension, palpitations, supraventricular tachyarrhythmias, syncope, tachycardia.

Central and peripheral nervous system: blepharospasm, dizziness, dysphonia, hypertonia, migraine, paresthesia, tremor, vertigo.

Gastrointestinal system: altered taste, anorexia, constipation, diarrhea, dyspepsia, flatulence, gastritis, hiccup, increased appetite, loose stools, nausea, vomiting.

Musculoskeletal system: arthralgia, myalgia.

Psychiatric: agitation, amnesia, anxiety, confusion, decreased libido, depression, impaired concentration, insomnia, irritability, paroniria.

Reproductive system: breast pain, dysmenorrhea, menorrhagia, vaginitis.

Respiratory system: bronchitis, bronchospasm, coughing, dyspnea, hemoptysis, laryngitis, nasal dryness, sinusitis, sneezing.

Skin and appendages: dermatitis, dry hair, dry skin, photosensitivity reaction, pruritus, purpura, urticaria.

Urinary system: altered micturition, urinary discoloration, urinary incontinence, urinary retention.

In addition, the following spontaneous adverse events have been reported rarely during the marketing of loratadine: abnormal hepatic function, including jaundice, hepatitis, and hepatic necrosis; alopecia; anaphylaxis; breast enlargement; erythema multiforme; peripheral edema; thrombocytopenia; and seizures.

Drug abuse and dependence: there is no information to indicate that abuse or dependency occurs with loratadine.

Overdose

In adults, somnolence, tachycardia, and headache have been reported with overdoses greater than 10 mg with the tablet formulation (40 mg-180 mg). Extrapyramidal signs and palpitations have been reported in children with overdoses of greater than 10 mg of Loratadine Syrup.

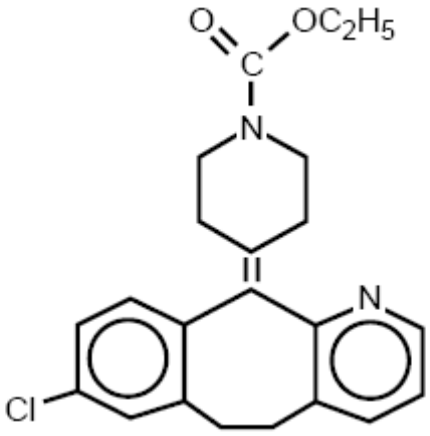
In the event of overdosage, general symptomatic and supportive measures should be instituted promptly and maintained for as long as necessary. Treatment of overdosage would reasonably consist of emesis (ipecac syrup), except in patients with impaired consciousness, followed by the administration of activated 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Loratadine is a non-sedating, long-acting tricyclic antihistamine with selective peripheral histamine H1-receptor antagonistic activity. It has a molecular weight of 382.89, and empirical formula of C22H23CIN2O2 its chemical name is ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate and has the following structural formula:



Loratadine exhibits an antihistaminic effect beginning within 1 to 3 hours, reaching a maximum at 8 to 12 hours, and lasting in excess of 24 hours.

Pharmacokinetic properties

Absorption: loratadine is rapidly absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations being attained in about 1 hour. Bioavailability is increased and time to peak plasma concentrations is delayed when taken with food.

Metabolism: loratadine is metabolized to descarboethoxyloratadine predominantly by cytochrome P450 3A4 (CYP3A4) and, to a lesser extent, by cytochrome P450 2D6 (CYP2D6). In the presence of a CYP3A4 inhibitor like ketoconazole, loratadine is metabolized to descarboethoxyloratadine predominantly by CYP2D6. Concurrent administration of loratadine with either ketoconazole, erythromycin (both CYP3A4 inhibitors), or cimetidine (CYP2D6 and CYP3A4 inhibitor) to healthy volunteers was associated with substantially increased plasma concentrations of loratadine.

Elimination: approximately 80% of the total loratadine dose administered can be found equally distributed between urine and feces in the form of metabolic products within 10 days. The mean elimination half-lives in normal adult subjects is 8.4 hours for loratadine and 28 hours for descarboethoxyloratadine. Loratadine and descarboethoxyloratadine reached steady-state in most patients by approximately the fifth dosing day.

Renal impairment: in subjects with chronic renal impairment (creatinine clearance ≤ 30 mL/min) both AUC and Cmax increased by approximately 73% for loratadine and by 120% for descarboethoxyloratadine, as compared to subjects with normal renal function (creatinine clearance ≥ 80 mL/min). The mean elimination half-lives of loratadine (7.6 hours) and descarboethoxyloratadine (23.9 hours) were not substantially different from those observed in normal subjects. Hemodialysis does not have an effect on the pharmacokinetics of loratadine or descarboethoxyloratadine in subjects with chronic renal impairment.

Hepatic Impairment: In patients with chronic alcoholic liver disease, the AUC and Cmax of loratadine were double while the pharmacokinetic profile of descarboethoxyloratadine was not substantially different from that observed in normal subjects. The elimination half-lives for loratadine and descarboethoxyloratadine were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

Geriatric: the AUC and peak plasma levels (Cmax) of both loratadine and descarboethoxyloratadine were approximately 50% greater than those observed in studies of younger subjects. The mean elimination half-lives for the geriatric subjects were 18.2 hours (range = 6.7 to 37 hours) for loratadine and 17.5 hours (range = 11 to 38 hours) for descarboethoxyloratadine.

Preclinical safety data

Carcinogenesis: AUC data demonstrated that the exposure of mice given 40 mg/kg of loratadine was 3.6 (loratadine) and 18 (descarboethoxyloratadine) times the exposure in adults and 5 (loratadine) and 20 (descarboethoxyloratadine) times the exposure in children given the maximum recommended daily oral dose. Exposure of rats given 25 mg/kg of loratadine was 28 (loratadine) and 67 (descarboethoxyloratadine) times the exposure in adults and 40 (loratadine) and 80 (descarboethoxyloratadine) times the exposure in children given the maximum recommended daily oral dose. Male mice given 40 mg/kg had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg, and males and females given 25 mg/kg. The clinical significance of these findings during long-term use of Loratadine is not known.

Mutagenicity: in mutagenicity studies, there was no evidence of mutagenic potential in reverse (Ames) or forward point mutation (CHO-HGPRT) assays, or in the assay for DNA damage (rat primary hepatocyte unscheduled DNA assay) or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenesis assay and the mouse bone marrow erythrocyte micronucleus assay).

Fertility: decreased fertility in male rats, shown by lower female conception rates, occurred at an oral dose of 64 mg/kg (approximately 50 times the maximum recommended human daily oral dose on a mg/m^2 basis) and was reversible with cessation of dosing. Loratadine had no effect on male or female fertility or reproduction in the rat at an oral dose of approximately 24 mg/kg (approximately 20 times the maximum recommended human daily oral dose on a mg/m^2 basis).

PHARMACEUTICAL PARTICULARS

List of excipients

Loratadine 10mg tablet: corn starch, colloidal silicon dioxide, talc, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, lactose monohydrate, povidone

Loratadine 5mg/5mL syrup: citric acid monohydrate, sodium benzoate, yellow color no.6 fdc ci 15985, sodium chloride, edetate disodium reagent grade, peach flavoring, glycerine, xanthan gum, propylene glycol, saccharin sodium, sorbitol solution 70%, hydrochloric acid reagent grade 37%, purified water q.s.

Incompatibilities

None known

Shelf life

Loratadine 10mg, tablet: 24 months

Loratadine 5mg/5mL, syrup: 36 months

Special precautions for storage

Loratadine 10mg, tablet: store between 2- 30°C

Loratadine 5mg/5mL, syrup: store between 2- 30°C

Nature and contents of container

Loratadine 10 mg, tablet: aluminum and amber PVC/PE/PVDC blister packages of 10, 20 and 30 Tablets.

Loratadine 5 mg/5 mL, syrup: amber sirop alpha glass 100 ml bottle with white aluminium cap marked with MK logo and pilfer- proof seal

Instructions for use / handling

None.

Manufacturer

Manufactured by Organon Heist BV

Heist-op-den-Berg,Belgium

DATE OF REVISION OF TEXT

CCDS version 1

19.01.2009