PRODUCT MONOGRAPH

LIBERATOR*

Extended Release Caplets
(loratadine 10 mg/pseudoephedrine sulfate 240 mg)

Histamine H_1 receptor antagonist/Sympathomimetic amine

Schering Canada Inc.
3535 Trans-Canada
Pointe-Claire, Quebec
H9R 1B4

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LIBERATOR
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(loratadine 10mg/pseudoephedrine sulfate USP 240mg)

THERAPEUTIC CLASSIFICATION

Histamine H_1 receptor antagonist/Sympathomimetic Amine

ACTIONS AND CLINICAL PHARMACOLOGY

Loratadine is a long-acting tricyclic antihistamine with selective peripheral H_1 receptor antagonistic activity. It exhibits a dose-related inhibition of the histamine-induced skin wheal and flare response in humans which is rapid in onset, is apparent at two hours and persists throughout the 24 hour observation period (Roman et al. 1986). Single oral doses up to 160 mg and repeat daily doses of 40 mg for up to 13 weeks were well tolerated with the incidence of sedation and dry mouth being no different from placebo.

^{14}C-loratadine is rapidly absorbed reaching Cmax values (4.7, 10.8 and 26.1 ng/mL) at 1.5, 1.0 and 1.3 hours for the 10, 20 and 40 mg dose, respectively. The loratadine elimination half-life (T-1/2ß) ranged from 7.8-11.0 hours.

Descarboethoxy-loratadine, the major active metabolite, reached Cmax values (4.0, 9.9 and 16.0 ng/mL) at 3.7, 1.5 and 2.0 hours after a dose of 10, 20 and 40 mg, respectively. Its T-1/2ß ranged from 17 to 24 hours. The accumulation indices, calculated by Cmax and the area under the curve (AUC) ratios did not change after the 5th day, indicating little or no accumulation of either loratadine or its metabolite after a multiple once per day dosage regimen. The T-1/2ß at steady state levels for loratadine and its active metabolite were 14.4 and 18.7 hours, respectively, similar to that reported following a single oral dose (Hilbert et al. 1987).

Approximately 82% of the ^{14}C-loratadine dose is excreted in the urine (40%) and feces (42%) over a 10-day period. Approximately 27% of the dose is eliminated in the urine during the first 24 hours largely in the conjugated form. Unchanged drug is present only in trace quantities in the urine and the active metabolite descarboethoxyloratadine represents only 0.4 to 0.6% of the administered loratadine dose.

Pseudoephedrine, 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 of the sympathetic nerves.

A drug interaction cross-over study was performed to compare LIBERATOR extended release caplets to the individual components (loratadine 10 mg and pseudoephedrine sulfate 240 mg). Coadministration of loratadine did not affect the bioavailability of pseudoephedrine. Similarly, coadministration of pseudoephedrine did not affect the pharmacokinetics of descarboethoxyloratadine although it resulted in the slightly higher (8%) bioavailability of loratadine: Cmax=2.79 ng/mL when administered in combination versus Cmax=2.55 ng/mL when administered alone. This is not considered to be of clinical significance.

Another study was conducted to characterize and compare the pharmacokinetic profile of loratadine, descarboethoxyloratadine and pseudoephedrine following oral administration of LIBERATOR given once daily and CLARITIN EXTRA (loratadine 5 mg / pseudoephedrine sulfate 120 mg) given every 12 hours. The results of this study show that after multiple doses to steady state, LIBERATOR and the CLARITIN EXTRA comparator were equivalent with respect to the bioavailability of loratadine and descarboethoxyloratadine (based on AUC), and bioequivalent for pseudoephedrine.

INDICATIONS AND CLINICAL USES

LIBERATOR (loratadine 10 mg/pseudoephedrine sulfate 240 mg) extended release caplets are indicated for the relief of symptoms associated with allergic rhinitis, including nasal and sinus congestion, sneezing, postnasal discharge and tearing and redness of the eyes. They are intended for short-term use only unless taken under medical supervision.

CONTRAINDICATIONS

LIBERATOR (loratadine 10 mg/pseudoephedrine sulfate 240 mg) extended release caplets are contraindicated in those patients who have shown sensitivity or idiosyncrasy to their components, to adrenergic agents or to other drugs of similar chemical structures. They are also contraindicated in patients receiving MAO inhibitor therapy or within 14 days of discontinuing such treatment and in patients with narrow-angle glaucoma, urinary retention, hypertension, severe coronary artery disease and hyperthyroidism.

PRECAUTIONS

General

Sympathomimetics should be used with caution in patients with stenosing peptic ulcer, pyloroduodenal obstruction, prostatic hypertrophy or bladder neck obstruction, cardiovascular disease, increased intraocular pressure or diabetes mellitus.

Sympathomimetics should be used with caution in patients receiving digitalis.

Sympathomimetics may cause central nervous system (CNS) stimulation and convulsions or cardiovascular collapse with accompanying hypotension.

Patients with severe liver impairment should be administered a lower initial dose because they may have reduced clearance of loratadine. For LIBERATOR, an initial dose of one caplet every other day is recommended.

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

Use in Elderly

In patients 60 years of age or older, sympathomimetics are also more likely to cause adverse reactions such as confusion, hallucination, convulsions, CNS depression and death. Consequently, caution should be exercised when administering a long-acting formulation to this patient group.

Dependence Liability

There are no data available to indicate that abuse or dependency occurs with loratadine.

Pseudoephedrine sulfate, like other CNS stimulants, has been abused. At high doses, subjects commonly experience mood elevation, decreased appetite and a sense of increased energy, physical strength, mental capacity and alertness. Anxiety, irritability and loquacity also have been reported. With continued use, tolerance develops; the user increases the dose and ultimately toxicity occurs. Depression may follow rapid withdrawal.

Use in Children

Safety and efficacy of LIBERATOR extended release caplets in children younger than 12 years of age have not yet been established.

Use in Obstetrics

The safe use of LIBERATOR extended release caplets during pregnancy or lactation has not been established and is therefore not recommended for use in pregnant or nursing mothers.

Nursing Mothers

Loratadine and its active metabolite are eliminated in the breast milk of lactating women with milk concentrations being similar to plasma concentrations. Through 48 hours after dosing, only 0.029% of the loratadine dose is eliminated in the milk as unchanged loratadine and its active metabolite, descarboethoxyloratadine.

Pseudoephedrine has been reported to be excreted into breast milk of lactating women. The use of LIBERATOR extended release caplets in nursing mothers is therefore not recommended.

Long-Term use

Because of the lack of experience with long-term use of this drug, its use should be limited to three months unless recommended by a physician.

Drug Interactions

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

When sympathomimetic drugs are given to patients receiving monoamine oxidase inhibitors (MAO), hypertensive reactions, including hypertensive crises, may occur. The antihypertensive effects of methyldopa, mecamylamine, reserpine and veratrum alkaloids may be reduced by sympathomimetics. Beta-adrenergic blocking agents may also 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. The antibacterial agent, furazolidone, is known to cause a dose-related inhibition of MAO. Although there are no reports of a hypertensive crisis caused by the concurrent administration of pseudoephedrine and furazolidone, they should not be taken together. Care should be taken in the administration of LIBERATOR concomitantly with other sympathomimetic amines because the combined effects on the cardiovascular system may be harmful to the patient.

Increase in plasma concentrations of loratadine have 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.

Drug/Laboratory Test Interactions:

Loratadine should be discontinued approximately 48 hours prior to skin testing procedures since antihistamines may prevent or diminish otherwise positive reactions to dermal reactivity indicators.

ADVERSE REACTIONS

Adverse experiences reported during the study with LIBERATOR (loratadine 10 mg/pseudoephedrine sulfate 240 mg) extended release caplets, administered once daily, were similar to those previously encountered during treatment with CLARITIN EXTRA tablets (loratadine 5 mg/pseudoephedrine sulfate 120 mg), administered twice daily. No unusual or unexpected adverse events were reported.

In clinical studies, the most frequently reported adverse events associated with LIBERATOR extended release caplets were headache, dry mouth, insomnia and somnolence.

Table 1

Number (%) of Patients Reporting Adverse Experiences (probably or possibly related to treatment) ≥5% incidence during treatment with LIBERATOR extended release caplets, Loratadine, Pseudoephedrine sulfate or placebo in clinical studies.

Adverse Experience	LIBERATOR	Loratadine	Pseudoephedrine Sulfate	Placebo
	(N=583)	(N=217)	(N=220)	(N=370)
Dry Mouth	55 (9)	7(3)	16(7)	11(3)
Headache	53 (9)	21(10)	21(10)	39(11)
Insomnia	38 (7)	2(1)	17(8)	4(1)
Somnolence	47 (8)	9(4)	9(4)	14(4)

Rarely reported events in decreasing order of frequency included dizziness, fatigue, anorexia, nervousness, nausea, epistaxis, rhinitis, lacrimal gland disorder, asthenia, hyperkinesia, constipation, dyspepsia, palpitation, tachycardia, thirst, agitation, irritability, coughing, dyspnea, nasal irritation, and pharyngitis.

With exception of headache, which was occasionally severe, most of the adverse events associated with LIBERATOR extended release caplets were mild to moderate in severity.

During the marketing of loratadine, alopecia, anaphylaxis, and abnormal hepatic function have been reported rarely.

There were rare postmarketing reports of mechanical upper gastrointestinal tract obstruction in patients taking the original round tablet formulation of LIBERATOR. In many of these cases, patients have had a history of difficulty in swallowing tablets, or had known upper gastrointestinal narrowing or abnormal esophageal peristalsis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In the event of overdosage, treatment, which should be started immediately, is symptomatic and supportive. Discontinuation of use, gastric lavage and support vital functions are advised.

Manifestations

Somnolence, tachycardia and headache have been reported with overdoses of loratadine.

Symptoms associated with overdoses of sympathomimetics 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 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

Adsorption of any drug in the stomach may be attempted by the administration of activated charcoal as a slurry with water. Gastric lavage should be considered. 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.

DOSAGE AND ADMINISTRATION

Adults and children 12 years of age and over:
One LIBERATOR (loratadine 10 mg/pseudoephedrine sulfate 240mg) extended-release caplet once daily taken whole with a glass of water, preferably upon waking. LIBERATOR may be taken without regard to mealtime.

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

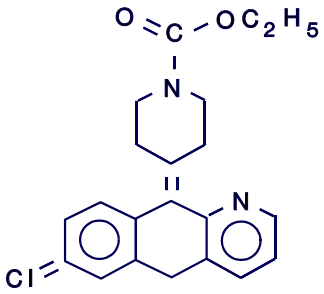
PHARMACEUTICAL INFORMATION

Drug substance

Proper name: loratadine (INN, USAN)

Chemical name: 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro- 11H-benzo[5,6]cyclohepta[1,2-ß] pyridin-11-ylidene)-, ethyl ester.

Structural formula:



Molecular formula: $C_{22}H_{23}ClN_2O_2$

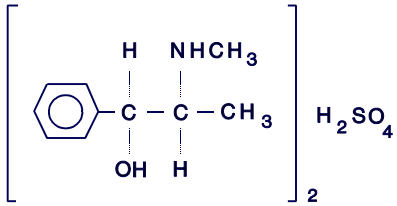
Molecular weight: 382.89

Appearance: White to off-white powder which melts between 131˚ and 137˚C.

Proper name: pseudoephedrine sulfate (USP)

Chemical name: Benzenemethanol, a-[1-(methylamino)-ethyl]-, [S-(R*,R*)]-, sulfate (2:1) (salt)

Structural formula:



Molecular formula: $(C_{10}H_{15}NO)_2.H_2SO_4$

Molecular weight: 428.54

Appearance: White to off-white crystals or powder.

Composition

LIBERATOR is an extended release caplet. Each LIBERATOR caplet contains 10 mg loratadine in the caplet coating and 240 mg pseudoephedrine sulfate in the extended-release core. The loratadine component is released immediately, whereas the pseudoephedrine sulfate component is released slowly from the core allowing for once daily administration.

The nonmedicinal ingredients in LIBERATOR extended release caplet coating include: hydroxypropyl methylcellulose 2910, polyethylene glycol 3350, polyethylene glycol 400, sucrose, white wax, carnauba wax and Opaspray White. The nonmedicinal ingredients in LIBERATOR extended release caplet core include: hydroxypropyl methylcellulose 2208, dibasic calcium phosphate dihydrate, ethylcellulose, povidone, silicon dioxide, magnesium stearate.

Storage conditions

Between 15˚ and 30˚C. Protect from exposure to excessive moisture.

AVAILABILITY OF DOSAGE FORM

Description: White, oval, biconvex, coated caplet.

Packaging: Blister packaged in 5's, 10's and 15's.

PHARMACOLOGY

Human Pharmacology

Pharmacokinetics

A randomised, single-dose, open-label, five-way crossover study was conducted in order to evaluate the bioavailability of loratadine and desloratadine following administration of five different CLARITIN formulations.

This study demonstrated that the mean Cmax and AUC values for loratadine and desloratadine were bioequivalent between the CLARITIN 10mg immediate release tablet and LIBERATOR extended release caplets.

Table 2
Arithmetic mean pharmacokinetic parameters of loratadine
and its major metabolite, desloratadine, for the CLARITIN 10 mg immediate release tablet
and LIBERATOR extended release caplet.

	CLARITIN 10 mg immediate release tablet	**LIBERATOR extended release caplet**
Loratadine		
Cmax (ng/ml)	3.12	3.68
AUC (ng . hr/ml)	8.76	9.34
Tmax (hr)	1.52	1.23
Desloratadine		
Cmax (ng/ml)	3.40	3.54
AUC (ng . hr/ml)	48.6	50.3
Tmax (hr)	2.06	1.79

A multiple-dose study was conducted to determine the steady-state bioequivalence of LIBERATOR extended release caplets administered once daily as compared to a reference standard consisting of loratadine 10 mg tablet given once daily and pseudoephedrine sulfate 120 mg CLARITIN EXTRA tablet in twice-a-day administration**.**

The results of the study showed that LIBERATOR extended release caplets and the reference standard were equivalent with respect to the bioavailability of pseudoephedrine, although the comparator in this study was a delayed-release pseudoephedrine sulfate formulation intended for twice-a-day dosing. LIBERATOR extended release caplets and the reference standard gave similar mean plasma concentrations for loratadine; however, no statistical conclusion regarding the bioequivalency could be made due to the low plasma drug concentrations and high intersubject variability.

A single-dose study was conducted to evaluate and compare the effect of food on the oral bioavailability of pseudoephedrine when administered as a LIBERATOR extended release caplet or a pseudoephedrine sulfate SR (sustained release) tablet. The bioavailability of pseudoephedrine from the LIBERATOR extended release caplet or the pseudoephedrine SR (sustained release) tablet was not affected significantly by food intake.

When administered with a high-fat meal, as compared with administration in a fasting state, the Cmax of pseudoephedrine was 22% higher from the LIBERATOR extended release caplet and 25% higher from the pseudoephedrine sulfate SR tablet: Cmax=304.5 ng/mL when pseudoephedrine was given after a 10-hour fast, Cmax=382.5 ng/mL when pseudoephedrine was given with breakfast and Cmax=376.6 ng/mL when pseudoephedrine + loratadine was given with breakfast. However, this difference is not considered to be clinically relevant.

A second food effect study was conducted with LIBERATOR extended release caplet. In this study, a standardized high-calorie, high-fat breakfast significantly increased the Cmax and AUC of loratadine by a mean of 53% and 76%, respectively, compared to the administration of LIBERATOR under fasted conditions ($p<0.05$). In contrast to loratadine, there was a very small and

non-significant increase in descarboethoxyloratadine Cmax and AUC values when LIBERATOR was given with food. Concomitant food slightly (7%) but significantly ($p<0.05$) increased the mean peak plasma pseudoephedrine concentrations, without significantly affecting the rate or extent of pseudoephedrine absorption.

Considering the magnitude of changes, the pharmacodynamics and safety of pseudoephedrine and loratadine, the increases in the plasma concentrations of these compounds that may occur when LIBERATOR is given with food are not expected to be clinically important.

A single-dose study was conducted to characterize the pharmacokinetic profile of pseudoephedrine following oral administration of three specially formulated loratadine/pseudoephedrine sulfate tablets with different in vitro release profiles and the standard LIBERATOR extended release caplet formulation. In vitro release profiles were characterized by "very fast", "fast", or "slow" dissolution tablets of loratadine/pseudoephedrine sulfate formulations. A positive correlation was obtained between in vitro dissolution rates and in vivo bioavailability of pseudoephedrine for varying formulations of loratadine/ pseudoephedrine sulfate.

Clinical Studies:

The efficacy of once-daily LIBERATOR was shown by its consistent pattern of superiority when compared with placebo in reducing the symptoms of seasonal allergic rhinitis. Total, total nasal, total nonnasal, rhinorrhea and nasal stuffiness symptom scores were significantly reduced ($p \leq 0.05$) in patients treated with LIBERATOR extended release caplets compared to placebo. When compared with its individual components, improvement in symptom scores in patients treated with LIBERATOR extended release caplets was consistently greater, numerically, than that seen in patients treated with either loratadine or pseudoephedrine alone.

The comparability of LIBERATOR extended release caplets to CLARITIN EXTRA was shown in two studies.

In one study, LIBERATOR and CLARITIN EXTRA were generally comparable in improving total nasal, total nonnasal and total symptom scores. LIBERATOR and CLARITIN EXTRA were significantly more effective than placebo in reducing composite scores at Day 4 and Endpoint ($p<0.05$).

In another study, LIBERATOR and CLARITIN EXTRA improvement in composite symptom scores was not different at key time points. Investigator evaluations of therapeutic response were consistent with symptom score evaluations.

TOXICOLOGY

Preclinical Data - Toxicity:

Loratadine/pseudoephedrine sulfate: In acute and single-dose studies, loratadine/pseudoephedrine sulfate tablets exhibited a low order of toxicity. Acute oral LD50 values ranged from approximately 600 mg/kg in mice to about 2000 mg/kg in rats. Cynomolgus monkeys tolerated single doses up to 240 mg/kg. Loratadine/pseudoephedrine sulfate tablets were no more toxic than either their individual components, and observed effects were generally related to the pseudoephedrine component.

Loratadine/pseudoephedrine sulfate tablets were administered orally for 3 months to rats and monkeys. Loratadine/pseudoephedrine sulfate tablets were well tolerated in rats at doses up to 200 mg/kg/day, which is 40 times the proposed maximum clinical dose. In monkeys, daily doses up to 50 mg/kg/day were also well tolerated. Severe toxicity was observed in monkeys at a dose of 125 mg/kg/day and was attributed to the effects of the pseudoephedrine component.

Loratadine

In acute and single-dose toxicity studies, loratadine exhibits a low order of toxicity. It is relatively well tolerated in rats and monkeys treated for periods up to 2 years. In these studies, rats received

oral doses of loratadine ranging from 2 to 240 mg/kg/day while monkeys were given doses ranging from 0.4 to 90 mg/kg/day.

Pseudoephedrine sulfate

This sympathomimetic agent is known to be less toxic and to produce less side effects than the ephedrine isomers, while being as potent as ephedrine as a bronchodilator and nasal decongestant.

Teratogenicity, mutagenicity and carcinogenicity

The combination loratadine/pseudoephedrine sulfate tablets was not teratogenic when administered orally to rats and rabbits during the period of organogenesis. The course of pregnancy or embryo/fetal viability of rats was not affected at doses up to 150 mg/kg/day (30 times the proposed clinical dose).

Loratadine/pseudoephedrine sulfate tablets did not directly affect embryo/fetal viability or offspring development of rabbits at doses up to 120 mg/kg/day.

Carcinogenicity, mutagenicity and teratology studies demonstrate that loratadine is not carcinogenic, mutagenic or teratogenic.

Likewise, pseudoephedrine sulfate is not considered to be carcinogenic, mutagenic or teratogenic. Therefore, loratadine/pseudoephedrine sulfate tablets are no more toxic than loratadine or pseudoephedrine sulfate alone.

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