

PRODUCT MONOGRAPH

CLARITIN[®] ALLERGY + SINUS

(5 mg Loratadine and 120 mg Pseudoephedrine Sulfate
Modified-Release Tablet)

Histamine H1 Receptor Antagonist/Sympathomimetic Amine

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DATE OF REVISION:
December 05, 2014

Control number: 179389

® TM see www.bayer.ca/tm-mc

PRODUCT MONOGRAPH

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(5 mg loratadine and 120 mg pseudoephedrine sulfate
modified-release tablets)

THERAPEUTIC CLASSIFICATION

Histamine H₁ receptor antagonist/Sympathomimetic Amine

ACTIONS

Loratadine is a long-acting tricyclic antihistamine with selective peripheral H₁ 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. 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.

¹⁴C-loratadine is rapidly absorbed reaching C_{max} 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_{1/2β}) ranged from 7.8-11.0 hours.

Descarboethoxy-loratadine, the major active metabolite, reached C_{max} 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_{1/2β} ranged from 17 to 24 hours. The accumulation indices, calculated by C_{max} 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_{1/2β} 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.

Approximately 82% of the ¹⁴C-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 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 of the sympathetic nerves.

INDICATIONS AND CLINICAL USES

CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets are indicated for the fast and long-lasting relief of nasal and ocular symptoms of upper respiratory mucosal congestion, such as in allergic rhinitis. They are intended for short-term use only unless taken under medical supervision.

CONTRAINDICATIONS

CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets 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, excitability 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; an initial dose of one tablet daily is recommended.

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 repeat-action 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 CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets in children younger than 12 years of age have not yet been established.

Use in Obstetrics: The safe use of CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets during pregnancy or lactation has not been established. The use of CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets during pregnancy is therefore not recommended.

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, descarboethoxy-loratadine. Pseudoephedrine has been reported to be excreted into breast milk of lactating women. The use of CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets in nursing mothers is therefore not recommended.

Other

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 (MAO) inhibitors, hypertensive reactions, including hypertensive crises, may occur. The antihypertensive effects of methyl dopa, 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 CLARITIN ALLERGY + SINUS concomitantly with other sympathomimetic amines because the combined effects on the cardiovascular system may be harmful to the patient.

Increases 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.

The in vitro addition of pseudoephedrine sulfate to sera containing the cardiac isoenzyme 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 CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets was comparable to that of placebo, with the exception of insomnia and dry mouth both of which were commonly reported. Other most frequently [$\geq 5\%$] reported adverse reactions associated with CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets, their components and placebo are listed on Table 1.

Rare adverse reactions in decreasing order of frequency included nausea, abdominal distress, anorexia, thirst, tachycardia, pharyngitis, rhinitis, acne, pruritus, rash, urticaria, arthralgia, confusion, dysphonia, hyperkinesia, hypoesthesia, decreased libido, paresthesia, tremor, vertigo, flushing, postural hypotension, increased sweating, eye disorders, earache, tinnitus, taste abnormality, agitation, apathy, depression, euphoria, paroniria, increased appetite, change in bowel habits, dyspepsia, eructation, hemorrhoids, tongue discoloration, tongue disorder, vomiting, transient abnormal hepatic function, dehydration, increased weight, hypertension, palpitation, migraine, bronchospasm, coughing, dyspnea, epistaxis, nasal congestion, sneezing, nasal irritation, dysuria, micturition disorder, nocturia, polyuria, urinary retention, asthenia, back pain, leg cramps, malaise and rigors.

As with other sympathomimetic amines, CNS stimulation, muscular weakness, tightness in the chest and syncope may also be encountered.

During the marketing of loratadine, alopecia, anaphylaxis (including angioedema), abnormal hepatic function, dizziness, palpitations and tachycardia have been reported rarely.

Very rare adverse events include convulsions or seizures which have been reported during the post-marketing of loratadine.

Table 1

Number (%) of Patients Reporting Adverse Experiences (probably or possibly related to treatment) $\geq 5\%$ incidence during treatment with CLARITIN ALLERGY + SINUS, either component alone (loratadine or pseudoephedrine) or placebo in clinical studies.

	A	B	C	D
Adverse Experience	CLARITIN ALLERGY + SINUS	Loratadine	Pseudoephedrine	Placebo
	(N=632)	(N=396)	(N=395)	(N=532)
Dizziness	27 (4)	4 (1)	10 (5)	8 (2)
Dry Mouth	93 (15)	17 (4)	41 (10)	21 (4)
Fatigue	26 (4)	22 (6)	14 (4)	13 (2)
Headache	64 (10)	48 (12)	34 (9)	52 (10)
Insomnia	113 (18)	16 (4)	66 (17)	20 (4)
Nervousness	33 (5)	11 (3)	30 (8)	5 (1)
Sedation	41 (6)	29 (7)	18 (5)	23 (4)

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

Manifestations

They 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

Emergency treatment should be started immediately. There is no specific antidote. Consider standard measures to remove any unabsorbed drug in the stomach, such as adsorption by activated charcoal administered as a slurry with water. The administration of 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 cleared by hemodialysis to any appreciable extent. 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:

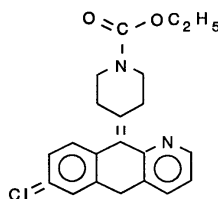
One CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablet twice a day.

PHARMACEUTICAL INFORMATION

Proper name: loratadine (INN, USAN)

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

Structural formula:



Molecular formula: C₂₂H₂₃ClN₂O₂

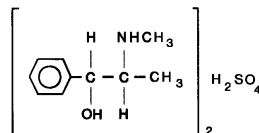
Molecular weight: 382.89

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

Proper name: Pseudoephedrine Sulfate (USP)

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

Structural formula:



Molecular formula: (C₁₀H₁₅NO)₂.H₂SO₄

Molecular weight: 428.54

Appearance: White to off-white crystals or powder.

Composition:

Each CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablet contains 5 mg loratadine in the tablet coating (immediate release) and 120 mg pseudoephedrine sulfate equally distributed between the tablet coating (immediate release) and the barrier-coated core (extended release). The two active components in the coating are quickly liberated; release of the decongestant in the core is delayed for several hours.

Other ingredients in the CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets include black ink, croscarmellose sodium, calcium phosphate dibasic, hypromellose, lactose, magnesium stearate, povidone, titanium dioxide.

Storage conditions:

Store between 15° and 30°C.

Dosage Form

Tablets containing 5 mg loratadine and 120 mg pseudoephedrine for oral use.

Description: White to off-white, film coated, round, extra deep convex tablet with “Claritin A+S” in black ink tablet.

Packaging: Blister packaged in 1's, 2's, 10's, 20's, and 30's.

CLINICAL PHARMACOLOGY

Pharmacodynamics: See under ACTIONS

Human Pharmacokinetics:

A two-way crossover study was conducted in 12 healthy male volunteers to determine the single-dose and steady-state bioequivalence of loratadine/pseudoephedrine sulfate tablets as compared to a control (a 5 mg loratadine capsule and a 120 mg pseudoephedrine sulfate tablet).

Each phase of the two-way crossover study consisted of two segments. In segment I, each volunteer received a loratadine/pseudoephedrine sulfate tablets (Treatment A) or control (Treatment B) on day 2 at 8 a.m. In segment II, each volunteer received Treatment A or B at 8 a.m. and 8 p.m. for 10 days. Plasma concentrations of pseudoephedrine sulfate were determined by high pressure liquid chromatography (HPLC) after single and multiple doses of the drug. Plasma concentrations of loratadine and its metabolite, descarboethoxyloratadine, were determined by radioimmunoassay (RIA) and HPLC, respectively, only after multiple doses. Plasma levels, AUC, C_{max} and T_{max} were analyzed via a cross-over analysis of variance in which effect of treatment, subject and phase were extracted. The results clearly establish the comparative bioavailability of loratadine/pseudoephedrine sulfate tablets to its components following a single dose and multiple (10 days) doses. There were no significant differences (<0.05) following single or multiple doses between Treatments A and B for AUC, C_{max} and T_{max} values (Table I). Comparative bioavailability and comparative clinical efficacy has been demonstrated between the loratadine/pseudoephedrine sulfate tablets and the control (a 5 mg loratadine capsule and a 120 mg pseudoephedrine sulfate tablet).

[See Table next page]

Table II

Mean (N=12) Pharmacokinetic Parameters of Loratadine and Pseudoephedrine Sulfate after Single and Multiple (10 Days Doses) Treatment

Loratadine/Pseudoephedrine sulfate

	<u>Tablets</u>	<u>Control</u>	<u>P-Value</u>
<u>Single-Dose Administration</u>			
Pseudoephedrine			
AUC (ng x hr/ml)	3922.21	3686.22	0.39
C _{max} (ng/ml)	284.60	262.15	0.40
T _{max} (hr)	6.33	6.50	0.81
<u>Multiple-Dose Administration</u>			
Pseudoephedrine			
AUC (ng x hr/ml)	6182.60	6343.31	0.71
C _{max} (ng/ml)	464.21	453.42	0.77
T _{max} (hr)	3.92	4.38	0.35
Loratadine			
AUC (ng x hr/ml)	4.98	3.89	0.06
C _{max} (ng/ml)	1.67	1.67	0.99
T _{max} (hr)	1.67	1.38	0.39
Descarboethoxyloratadine			
AUC (ng x hr/ml)	83.31	117.16	0.25
C _{max} (ng/ml)	5.15	5.20	0.95
T _{max} (hr)	2.55	5.95	0.34

Comparative Bioavailability Study:

Open-label, randomized, 4-period crossover study comparing the bioequivalence of a single dose of the test formulation (loratadine 5 mg/pseudoephedrine sulfate 120 mg; 12-Hour Extended Release Tablet) to a single dose of Claritin® Allergy + Sinus (Reference formulation, loratadine 5 mg/pseudoephedrine sulfate 120 mg; 12-Hour Extended Release Tablet) under fasted and fed conditions. The study was performed on 54 healthy adult subjects with a washout phase of 14 days between doses.

SUMMARY TABLES OF THE COMPARATIVE BIOAVAILABILITY DATA

Loratadine (Fasted Condition) (1 x 5 mg) From measured data uncorrected for potency Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (pg·hr/mL)	3132.1 4902.3 (129.68)	3194.5 4928.8 (117.41)	96.33	89.32 - 103.89
AUC _I (pg·hr/mL)	3419.3 5361.8 (128.21)	3488.2 5397.6 (116.53)	96.29	89.18 - 103.96
C _{max} (pg/mL)	1330 1830 (92.8)	1150 1650 (99.3)	114.91	103.20 - 127.96
T _{max} § (h)	1.00 (0.995 - 1.50)	1.50 (0.998 - 5.00)		
T _{1/2} (h)	10.1 (122)	11.0 (114)		

* Test = Claritin-D 12-Hour Extended Release Tablet (loratadine 5 mg/pseudoephedrine sulfate 120 mg)

† Reference = Claritin Allergy + Sinus (loratadine 5 mg/pseudoephedrine sulfate 120 mg) (Canada)

§ Expressed as the median (min-max)

Loratadine (Fed Condition) (1 x 5 mg) From measured data uncorrected for potency Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (pg·hr/mL)	5711.0 7480.8 (85.712)	6008.1 8274.9 (95.307)	95.29	88.39 - 102.71
AUC _I (pg·hr/mL)	6298.1 8239.9(84.393)	6483.1 8975.8 (94.957)	95.77	88.62 - 103.50
C _{max} (pg/mL)	1380 1770 (72.2)	1520 1970 (75.4)	91.03	81.81 - 101.30
T _{max} [§] (h)	2.50 (1.00 - 5.00)	2.50 (1.50 - 6.00)		
T _{1/2} (h)	15.2 (84.4)	15.0 (88.2)		

* Test = Claritin-D 12-Hour Extended Release Tablet (loratadine 5 mg/pseudoephedrine sulfate 120 mg)

† Reference = Claritin Allergy + Sinus (loratadine 5 mg/pseudoephedrine sulfate 120 mg) (Canada)

§ Expressed as the median (min-max)

Pseudoephedrine (Fasted Condition) (1 x 120 mg) From measured data uncorrected for potency Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng·hr/mL)	4147 4242 (21.81)	4054 4197 (26.43)	102.21	98.73 - 105.82
AUC _I (ng·hr/mL)	4208 4303 (21.61)	4104 4244 (26.13)	101.38	98.15 - 104.71
C _{max} (ng/mL)	377 383 (17.2)	366 373 (19.5)	103.39	99.36 - 107.58
T _{max} § (h)	5.00 (3.50 - 8.00)	5.50 (2.00 - 10.0)		
T _½ (h)	5.10 (17.0)	5.04 (19.8)		

* Test = Claritin-D 12-Hour Extended Release Tablet (loratadine 5 mg/pseudoephedrine sulfate 120 mg)

† Reference = Claritin Allergy + Sinus (loratadine 5 mg/pseudoephedrine sulfate 120 mg) (Canada)

§ Expressed as the median (min-max)

Pseudoephedrine (Fed Condition) (1 x 120 mg) From measured data uncorrected for potency Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng·hr/mL)	3744 3842 (23.80)	3930 4080 (28.05)	95.05	91.81 - 98.41
AUC _I (ng·hr/mL)	3808 3905 (23.47)	3976 4125 (27.81)	94.61	91.59 - 97.72
C _{max} (ng/mL)	403 411 (20.3)	384 394 (22.4)	104.43	100.36 - 108.67
T _{max} ‡ (h)	5.00 (3.00 - 12.0)	6.00 (4.50 - 8.04)		
T _½ (h)	4.74 (15.7)	4.97 (20.7)		

* Test = Claritin-D 12-Hour Extended Release Tablet (loratadine 5 mg/pseudoephedrine sulfate 120 mg)

† Reference = Claritin Allergy + Sinus (loratadine 5 mg/pseudoephedrine sulfate 120 mg) (Canada)

‡ Expressed as the median (min-max)

Clinical Studies

The efficacy and safety of CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release Tablets were studied in well controlled comparative trials against loratadine 5 mg, pseudoephedrine sulfate 120 mg and placebo.

Efficacy Evaluation Parameters

Multicentric, randomized, double-blind, paralleled-group studies were conducted during the Fall and Spring allergy seasons in various geographic areas with patients having signs and symptoms of seasonal allergic rhinitis. Antigen skin tests were conducted prior to the start of the study to confirm patients' hypersensitivity to the seasonal pollens indigenous to the geographic area. Study medications and placebo were administered orally twice daily for 14 days in four studies and for 28 days in one study. Nasal signs and symptoms considered for evaluation included nasal discharge, stuffiness, itching and sneezing. Non-nasal signs and symptoms such as itching, tearing, redness of eyes and itching of ears or palate were also evaluated. Severity of individual signs and symptoms was measured at baseline and at days 4,8 and 15 in the 14-day studies and weekly in the 28-day study. The primary efficacy variable was the change from baseline in total symptom score at the previously specified time points during therapy. The major time points used to determine efficacy were the first treatment evaluation (study day 4 in the 14-day studies and week 1 in the 28-day study) and the endpoint evaluation which was defined as the patient's last valid evaluation in the study.

I. Total Symptom Scores - Fall Studies

In both studies conducted during the Fall allergy season, patients treated with CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets demonstrated a statistically significant decrease ($p < 0.05$) in total symptom score, as well as in total nasal and non-nasal symptoms when compared with placebo-treated patients at both day 4 and endpoint evaluations.

When compared with the individual active components, one of these studies showed that CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets were significantly more effective ($p < 0.05$) than loratadine and pseudoephedrine sulfate alone in reducing overall total and total nasal symptoms. Furthermore, CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets were as effective as loratadine and significantly more effective [$p < 0.05$] than pseudoephedrine sulfate in reducing total non-nasal symptoms at both day 4 and endpoint evaluations.

I. Total Symptom Scores - Spring Studies

In these two studies patients treated with CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets showed a statistically significant decrease ($p < 0.05$) ($p < 0.01$) in total symptom score and in total nasal and non-nasal symptoms when compared with placebo-treated patients at both the initial and endpoint treatment evaluations.

In one of the studies CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets were significantly more effective ($p < 0.04$) than loratadine in reducing overall total symptoms and total nasal symptoms at endpoint evaluation. In addition, a separate analysis of treatment effects was conducted for those patients who had high and low total symptom scores at baseline. This analysis was performed to differentiate clearly the contribution of each active component to the efficacy of CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets. In patients with more severe baseline total symptoms, CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets were considerably better than pseudoephedrine sulfate in reducing total symptoms and total non-nasal symptoms. A trend towards a statistically significant effect favouring CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets over pseudoephedrine sulfate was evident in the reduction of total nasal symptoms.

Results of the other study demonstrated that at both day 4 and endpoint evaluations, CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets were significantly better ($p \leq 0.01$) than loratadine and pseudoephedrine sulfate in reducing mean total symptom scores. At the endpoint evaluation, mean decreases in total nasal and non-nasal symptoms were also statistically significant ($p \leq 0.05$) in those patients treated with CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets.

In the other study, results also indicated that when compared with the individual components CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets were significantly more effective ($p < 0.05$) than loratadine and pseudoephedrine sulfate alone in relieving nasal and non-nasal symptoms of seasonal allergic rhinitis.

A 28-day study corroborated further the findings of the Fall and Spring 14-day studies. CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets were consistently and statistically ($p < 0.05$) more effective than placebo in decreasing mean total, total nasal and total non-nasal symptoms scores at both week 1 and endpoint evaluations. Magnitudes of symptom improvement with both CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets and placebo were similar to those observed in the previous studies. Moreover, effects of symptom relief with CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets were maintained throughout the four-week treatment course.

II. Nasal Stuffiness Symptom Scores

The effects of CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets on nasal stuffiness, the symptom most likely to respond to treatment with pseudoephedrine sulfate, were assessed separately in all studies. Mean percent reduction in nasal stuffiness scores in patients treated with CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets ranged from 40% to 48% in the Fall studies and from 41% to 55% in the Spring studies. In most cases, CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets were significantly more effective ($p < 0.05$) than placebo in reducing this symptom.

Moreover, pseudoephedrine sulfate was significantly more effective ($p < 0.05$) than placebo in three of the four studies, while loratadine alone was not significantly better than placebo in any of the studies. CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets were comparable or slightly superior to pseudoephedrine sulfate alone in reducing nasal stuffiness.

Safety

CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets were well tolerated in all patients. No serious or unusual adverse experiences were reported with any of the study medications. No clinically meaningful changes from baseline were observed in either vital sign determinations during treatment or in post-treatment laboratory tests in any of the studies.

In summary, the results of these clinical trials clearly demonstrate that CLARITIN ALLERGY + SINUS (loratadine & pseudoephedrine sulfate) modified-release tablets are safe and more effective than either of its components alone or placebo in the treatment of patients with seasonal allergic rhinitis.

TOXICOLOGY

Preclinical Data - Toxicity:

Loratadine/pseudoephedrine sulfate

In acute and single-dose studies, loratadine & pseudoephedrine sulfate modified-release 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 modified-release tablets were administered orally for 3 months to rats and monkeys. Loratadine & pseudoephedrine modified-release 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

During long-term loratadine toxicity studies conducted in mice, rats and monkeys, changes were observed in reproductive organs of male rats, consisting of weight reduction of the prostate gland and the testes; those changes were without consequence after a recovery period of 28 days. Similar changes in the male rat have been observed after administering drugs like antazoline, dexchlorpheniramine, meclozine, phenbenzamine and pyribenzamine.

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

Loratadine & pseudoephedrine sulfate modified-release tablets were 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 modified-release 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 modified-release tablets are no more toxic than loratadine or pseudoephedrine sulfate alone.

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PART III: CONSUMER INFORMATION**CLARITIN® ALLERGY + SINUS**

(5 mg Loratadine and 120 mg Pseudoephedrine Sulfate Modified-Release Tablet)

This leaflet is part III of a "Product Monograph" published when CLARITIN® ALLERGY + SINUS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CLARITIN® ALLERGY + SINUS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

CLARITIN® ALLERGY + SINUS provide:

- Fast and long-lasting relief of symptoms from indoor (dust mites, pet dander and moulds) and outdoor (tree, grass, and ragweed pollens) allergies (allergic rhinitis) including itchy, watery, red burning eyes; sneezing, runny nose, itchy nose, and nasal congestion, sinus pressure and sinus congestion.

What it does:

CLARITIN® ALLERGY + SINUS is a fast acting and long-lasting antihistamine + decongestant that contains:

- an antihistamine (loratadine), which—blocks the action of histamine and relieves allergy symptoms. When you are exposed to indoor and or outdoor allergens your body responds by releasing histamine. Histamine causes allergy symptoms such as itchy, watery, red burning eyes; sneezing, runny nose, and itchy nose.
- a decongestant (pseudoephedrine sulfate) that relieves nasal congestion, sinus pressure and sinus congestion due to allergies by constricting the blood vessels in the lining of the nose and sinuses.

One dose of CLARITIN® ALLERGY + SINUS provides 12 hour relief of allergy symptoms.

When it should not be used:

CLARITIN® ALLERGY + SINUS should not be used if you are/have:

- allergic to loratadine, pseudoephedrine or to any of the other product ingredients (see What the important non-medicinal ingredients are).
- taking a monoamine oxidase (MAO) inhibitor or stopped taking one less than two weeks ago
- narrow-angle glaucoma (increased pressure in the eye)

- difficulty urinating due to enlargement of the prostate gland
- high blood pressure
- hyperthyroidism (overactive thyroid)
- heart disease

What the medicinal ingredients are:

- Loratadine
- Pseudoephedrine sulfate

What the important non-medicinal ingredients are:

CLARITIN® ALLERGY + SINUS (in alphabetical order): black ink, croscarmellose sodium, calcium phosphate dibasic, hypromellose, lactose, magnesium stearate, povidone, titanium dioxide.

What dosage forms it comes in:

Modified-release tablets: containing 5 mg loratadine for immediate release & 120 mg pseudoephedrine sulfate for immediate and extended release.

WARNINGS AND PRECAUTIONS

BEFORE you use CLARITIN® ALLERGY + SINUS talk to your doctor or pharmacist if any of the following conditions applies to you:

- pregnant or nursing
- elderly
- taking other medications
- liver or kidney disease
- diabetes
- stomach problems

Stop use and ask a doctor if:

- symptoms do not improve within 7 days or are accompanied by a fever.
- nervousness, dizziness or sleeplessness occurs.

Stop taking CLARITIN® ALLERGY + SINUS 48 hours prior to any skin testing procedures.

INTERACTIONS WITH THIS MEDICATION

The drugs that may interact with CLARITIN® ALLERGY + SINUS: monoamine oxidase inhibitors, methyl dopa, mecamylamine, reserpine and veratrum alkaloids, beta-adrenergic blocking agents, digitalis, antacids, kaolin, furazolidone, ketoconazole, erythromycin, cimetidine or other sympathomimetic amines, it is important to ask your doctor or pharmacist before taking CLARITIN® ALLERGY + SINUS.

PROPER USE OF THIS MEDICATION

Usual dose:

- **Adults and adolescents (12 years of age and older):** one tablet every 12 hours. Do not exceed more than two tablets in 24 hours. Do not crush, break, chew or dissolve the tablet. Swallow whole with water.
- Limited to 3 months of use unless recommended by a doctor.

Overdose:

In case of drug overdose, contact your Poison control Centre, physician or pharmacist as soon as possible, even if there are no symptoms.

Missed Dose:

If you miss taking your dose on time, do not worry; take your dose when you remember.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its desired effects, CLARITIN® ALLERGY + SINUS may cause undesirable effects.

Side effects that may occur include dizziness, dry mouth, fatigue, headache, insomnia, nervousness, sedation. If these side effects do not go away or worsen, stop use and call your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk to your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rarely	Allergic reaction (rash, swelling, difficulty in breathing)			√
	Fast heart rate or heart palpitations			√
	Liver dysfunction			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk to your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Rare	Convulsions or Seizures			√

This is not a complete list of side effects. For any unexpected effects while taking CLARITIN® ALLERGY + SINUS, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15° and 30°C.

Keep this and all medication stored in a safe place and of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
 - Call toll-free at 1-866-234-2345
 - Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9
- Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Bayer Inc., at: 1 800-714-4449

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Last revised: December 05, 2014
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