

PRODUCT MONOGRAPH

Pr **LIVOSTIN[®]***

levocabastine Nasal Spray

0.5 mg/mL as levocabastine hydrochloride

Histamine H₁-antagonist

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CLINICAL PHARMACOLOGY

LIVOSTIN® levocabastine hydrochloride is a potent, fast-acting and highly selective histamine H₁-antagonist with a sustained duration of action.

Within 10 minutes of topical application to the nose, levocabastine inhibits sneezing, itchy nose and rhinorrhea induced by nasal provocation with allergens.

Orally administered levocabastine provides a dose-dependent inhibition of skin reactions to intradermal histamine. After repeated topical application to the nose, topical and systemic antihistamine effects contribute to overall clinical outcome. Although systemic effects may contribute to the therapeutic effects of levocabastine nasal spray, this is not accompanied by any sedative effects.

Levocabastine nasal spray (2 sprays/nostril t.i.d.), under acute and steady-state conditions, is devoid of CNS effects, as evaluated by objective and subjective psychoperformance tests and measures of general CNS activity.

Following topical application to the nose, the absorption of levocabastine was incomplete and the absolute bioavailability of levocabastine administered in the nose could be estimated at 60-80% in healthy volunteers and in patients with allergic rhinitis.

INDICATIONS AND CLINICAL USE

LIVOSTIN® levocabastine hydrochloride nasal spray is indicated for the symptomatic treatment of allergic rhinitis (sneezing, itchy nose, runny nose) in patients 12 years of age and older.

CONTRAINDICATIONS

LIVOSTIN[®] levocabastine hydrochloride nasal spray is contraindicated in patients with hypersensitivity to any of the ingredients.

WARNINGS

Use in Pregnancy and Lactation

There are no clinical trials on the use of LIVOSTIN[®] levocabastine hydrochloride nasal spray in pregnant or nursing women; therefore, LIVOSTIN[®] nasal spray should not be used during pregnancy, except if the potential benefit justifies the potential risk to the fetus.

LIVOSTIN[®] can be excreted in human milk. Administration of LIVOSTIN[®] nasal spray to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Use in Children

LIVOSTIN[®] is not recommended for use in children under the age of 12 years. Clinical experience with nasal LIVOSTIN[®] is absent in children under 5 years of age.

Effects on Driving Ability and Use of Machinery

LIVOSTIN[®] levocabastine hydrochloride nasal spray will generally not cause clinically relevant sedation nor does it impair psychomotor performance as compared with placebo. LIVOSTIN[®] nasal spray, therefore, would not be expected to interfere with the ability to drive a car or operate machinery. Should drowsiness occur, caution is advised.

PRECAUTIONS

Renal

Limited data are available on the use of levocabastine in patients with renal impairment. Caution should be exercised when administering LIVOSTIN[®] levocabastine hydrochloride nasal spray to patients with renal impairment (see **Pharmacokinetics**).

Use in the Elderly

The safety and efficacy of topical levocabastine has not been established in patients older than 65 years of age.

Drug Interactions

Interactions with alcohol or any other drugs were never reported in clinical trials. In specifically designed studies, there was no evidence of potentiation of the effects of either alcohol or diazepam by LIVOSTIN[®] nasal spray used in normal dosages.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

The most frequent side effect encountered with LIVOSTIN[®] levocabastine hydrochloride nasal spray during clinical trials is nasal irritation. Most side effects are transient and rarely necessitate discontinuation of therapy.

Table 1 lists instances of frequent adverse experiences observed during clinical trials.

Post-Market Adverse Drug Reactions

In addition to the side effects identified in clinical trials (see Table 1), the following post-marketing adverse drug reactions have been very rarely reported: hypersensitivity, dyspnoea, bronchospasm, tachycardia, nasal congestion, epistaxis, headache, eyelid edema, fatigue, malaise, and application site reactions including nasal edema and nasal discomfort. In post-marketing experience, allergic reactions have rarely been reported.

Table 1: Incidence of the most frequent⁺ adverse experiences in patients treated with LIVOSTIN[®] nasal spray or placebo nasal spray.

ORGAN SYSTEM	INCIDENCE (%)	
	LIVOSTIN [®] Nasal Spray (n=702)	PLACEBO Nasal Spray (n=427)
<u>Respiratory System</u>	<u>10.4</u>	<u>9.6</u>
nasal irritation	5.4	5.6
epistaxis	1.0	<1.0
<u>Central Nervous System</u>	<u>7.7</u>	<u>7.0</u>
somnolence	3.8	3.5
headache	3.1	3.0
dizziness	<1.0	<1.0
<u>Ocular</u>	<u>3.0</u>	<u>2.1</u>
eye irritation ⁺⁺	2.6	1.9
<u>Other</u>		
dry mouth	3.3	2.6
tiredness	1.4	<1.0

Coughing, throat irritation, respiratory disorder, aggravated nasal obstruction and nasal pruritus were <1.0% in the LIVOSTIN[®] group and not reported in the PLACEBO group. The others (dry nose, rhinorrhea, dyspnea, itchy throat) were <1.0% for both the LIVOSTIN[®] and PLACEBO groups.

Facial edema, rash, decreased hearing, pruritus of external ear and taste perversion were <1.0% in the LIVOSTIN[®] group and not reported in the PLACEBO group. The others (abdominal pain, increased appetite, nausea and increased weight) were <1.0% for both the LIVOSTIN[®] and PLACEBO groups.

⁺ Reported more than once in the LIVOSTIN[®] group.

⁺⁺ The eye irritation observed in the levocabastine nasal spray group was mostly reported by the patients receiving both the levocabastine nasal spray and eye drops.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been no reports of overdosage of LIVOSTIN[®] levocabastine hydrochloride nasal spray. Some sedation after accidental intake of the contents of the bottle cannot be excluded.

In the case of accidental ingestion, the patient should be advised to drink plenty of non-alcoholic fluids in order to accelerate the renal elimination of levocabastine hydrochloride. Treatment of overdosage should include general supportive measures.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Adults and children (12 to 65 years old): the usual dose is 2 sprays (50 µg/spray) of LIVOSTIN[®] levocabastine hydrochloride nasal spray per nostril, 2 times daily. The dose may be increased to 2 sprays 3 to 4 times daily.

It is not useful to continue the treatment for more than 3 days if no improvement is seen. There are no clinical studies to support continuous treatment durations of greater than 10 weeks.

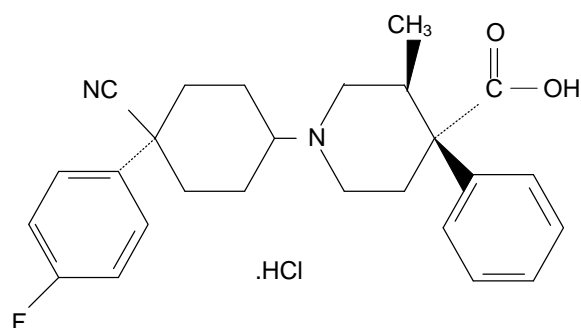
As LIVOSTIN[®] nasal spray is available as a microsuspension, the bottle should be shaken before each application. Patients should be instructed to clear the nasal passages prior to administering the spray and to inhale through the nose during spraying. Before using the pump delivery system for the first time, the pump reservoir should be filled up by priming until a fine spray is delivered.

PHARMACEUTICAL INFORMATION

Drug Substance

Trade Name: LIVOSTIN[®]
Common Name: levocabastine hydrochloride
Chemical Name: (-)-[3s-[1(cis),3 α ,4 β]]-1-[4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenyl-4-piperidine carboxylic acid monohydrochloride

Chemical Structure:



Molecular Formula: C₂₆H₂₉FN₂O₂·HCl

Molecular Weight: 456.99

Description: Levocabastine hydrochloride is a white to almost-white powder with a melting temperature of >300EC, a pK_{a1} of 3.1 and a pK_{a2} of 9.7. It is freely soluble in dimethylsulfoxide; soluble in N,N-dimethylformamide and methanol; slightly soluble in propylene glycol, polyethylene glycol and ethanol; in aqueous medium the solubility is a function of pH, with minimum solubility at pH 4.1 to 9.8. The log-partition coefficient (n-octanol/aqueous buffer at pH 8.0) is 1.82.

Composition

LIVOSTIN[®] levocabastine hydrochloride nasal spray is available as a microsuspension (pH 6-8). Each mL contains levocabastine hydrochloride (equivalent to 0.5 mg levocabastine) as active ingredient; benzalkonium chloride 0.15 mg as preservative; and propylene glycol, polysorbate 80, disodium phosphate, monosodium phosphate, disodium edetate, hypromellose and water as inactive excipients.

Stability and Storage Recommendations

LIVOSTIN[®] nasal spray should be stored at room temperature (15EC-30EC).

AVAILABILITY OF DOSAGE FORM

LIVOSTIN[®] levocabastine hydrochloride nasal spray is available in 15 mL plastic bottles containing 15 mL of white microsuspension.

PHARMACOLOGY

Pharmacodynamics

LIVOSTIN[®] levocabastine hydrochloride is a structurally novel histamine H₁-antagonist.

All *in vivo* studies, as well as studies on isolated tissues and on receptors, point to a single action responsible for the antiallergic activity of levocabastine: fast and tight high affinity binding to H₁-receptors.

In Vivo:

In rats, guinea pigs and dogs, levocabastine, administered systemically, was a potent inhibitor of histamine effects known to be mediated by H₁ receptors (see Table 2). Levocabastine had a fast onset of action (within one hour) and remained active for about 24 hours, at doses below 0.010 mg/kg.

Table 2: Activity of levocabastine in various models of allergic reactions

<u>Animal</u>	<u>Test</u>	<u>Active Dose or Concentration</u>
Guinea pigs	Histamine-induced lethality	ED ₅₀ (p.o.) 0.0009 mg/kg
Guinea pigs	Histamine-induced dyspnea reaction	ED ₅₀ (p.o.) 0.005 mg/kg
Guinea pigs	Histamine-induced bronchoconstriction	ED ₅₀ (i.v.) 0.005 mg/kg
Rats	Compound 48/80 lethality	ED ₅₀ (p.o.) 0.0020 mg/kg
Dogs	Ascaris allergen skin reaction	ED ₅₀ (p.o.) 0.0035 mg/kg

The mode of action of levocabastine appears to be remarkably selective, as it is devoid of protection against dyspnea reactions induced by aerosolized serotonin and acetylcholine at a dose 500 times the effective dose for histamine aerosols.

In rats, single oral doses up to 160 mg/kg showed no interference with neurotransmission (mediated by acetylcholine, serotonin, dopamine or GABA), no change in normal body functions (such as food consumption and locomotor activity), and in a series of responses (such as inflammatory and cardiovascular responses). The most pronounced activity found was induction of palpebral ptosis at 65.1 mg/kg (46,500 times the antiallergic dose).

At 6.36 mg/kg of levocabastine, apomorphine-induced emesis was antagonized in dogs, and peripheral dopamine antagonism (exemplified by increased prolactin levels in female mice) was found upon repeated administration of high toxicological doses (12.9 and 52 mg/kg).

In dogs, doses of 0.16 mg/kg orally and 0.5 mg/kg i.v. of levocabastine had no significant effect on sleep-wakefulness patterns, nor on cardiac, hemodynamic, or respiratory parameters. Similarly in anaesthetized dogs, cumulative doses up to 0.50 mg/kg had no cardiac or hemodynamic effect.

In Vitro:

A high level of selectivity with levocabastine was found *in vitro*, in biochemical studies (neurotransmitter receptor and uptake) and experiments on isolated tissues where the observations were extended to β -adrenergic and peptide interactions and to interference with myogenic activity.

Levocabastine inhibited almost equipotently the contractile activity of guinea pig trachea (ED_{50} of 0.0081 mg/L) and ileum (ED_{50} of 0.0316 mg/L) induced by histamine. At a concentration of 10^{-5} M, levocabastine did not induce histamine release, nor did it inhibit antigen-induced histamine release from rat peritoneal mast cells. Receptor binding experiments showed that levocabastine strongly ($K_i=4.2$ nM, with 240 minutes incubation time) interfered with the binding of 3H -pyrilamine to the guinea pig cerebellum. Levocabastine was also found to occupy histamine H_1 -receptors in the lungs at very low doses.

Levocabastine was devoid of effect in tests which measure interference with microsomal enzymes. Its potential for drug interaction appears to be extremely low.

Pharmacokinetics

A comparison of the pharmacokinetic parameters of levocabastine in male rats, rabbits, dogs and man was carried out following a single intravenous administration (Table 3). The apparent volume of distribution ($V_{d_{ss}}$) and the fraction of drug not bound (f_u) by plasma proteins were very similar in rats, dogs, rabbits and man. The plasma clearance, though, in humans was four to six times lower than in the three animal species. As a consequence, the elimination half-life was longer in humans (35-40 hours as compared to 6 hours in rats, 10 hours in rabbits and 12 hours in dogs). Also the AUC values and the steady-state plasma levels, when normalized for the dose, were larger in humans than in the animal species. In man, the pharmacokinetics, following single intravenous administration of 0.2 mg levocabastine, could be described by a two-compartment open model although the contribution of the distribution phase was only 1.2% of the total plasma concentration-time curve.

Table 3: Comparison of pharmacokinetic parameters of levocabastine in male rats, rabbits, dogs and man after single intravenous administration

PARAMETER	RAT	RABBIT	DOG	MAN
Dose (mg/kg)	0.1	0.1	0.2	0.0027
$t_{1/2\alpha}$ (h)	0.36	1.72	0.96	0.59
$t_{1/2\beta}$ (h)	6.0	10.1	12.2	32.9
Cl_t (mL.h ⁻¹ .kg ⁻¹)	162	163	111	25.1
V_c (L.kg ⁻¹)	0.92	1.02	1.24	0.60
$V_{d_{ss}}$ (L.kg ⁻¹)	1.36	1.73	1.83	1.13
$V_{d\beta}$ (L.kg ⁻¹)	1.40	2.35	1.95	1.15
AUC _{0-∞} (ng.mL ⁻¹ .h)	670	624	1836	115
AUC _{0-∞} normalized to 0.1 mg/kg	670	624	918	4259
f_u (%)	46.5	53.2	52.8	55.3

Following single oral administration, levocabastine was well absorbed in all species studied, and the bioavailability was complete in humans and dogs. Following a single oral administration of 0.5, 1 and 2 mg levocabastine to healthy volunteers, there was rapid and complete absorption with a T_{max} of 2 hours and the absolute bioavailability of 101-120%.

After intranasal application of a 50 µg/puff dose, about 30-45 µg of levocabastine is absorbed. Levocabastine reaches peak plasma levels about 3 hours after nasal administration.

On repeated administration, steady-state was reached within 2-6 days in rats and dogs and within 7 days in humans. Average steady-state levels of levocabastine increased proportionally with the dose after intravenous administration in rats and dogs (0.05 to 0.2 mg/kg) and after oral administration in rats and mice (2.5 to 40 mg/kg) and in dogs (5 to 20 mg/kg). In man, the plasma concentrations following chronic nasal application of levocabastine are linear and predictable from single-dose data. The absorption of levocabastine through the nasal mucosa, and the systemic disposition in terms of distribution and elimination are not altered during repeated dosing.

Levocabastine was rapidly and fairly evenly distributed to the various tissues. In rats, levels in most tissues were similar to four times higher than the corresponding plasma levels. The lowest levels (three to eight times lower than plasma) occurred in the brain and the highest in the liver (six times higher than in plasma). After oral administration in rats, there was a remarkable uptake in the nasal cavity and lacrimal glands. In pregnant rats, there was a rapid equilibrium between the maternal and fetal tissues and body fluids after intravenous and oral administration. The maternal and fetal radioactivity consisted exclusively of unchanged levocabastine at all time points and disappeared from maternal and fetal tissues with the same half-life as from plasma.

After a single oral dose of ³H-levocabastine, plasma radioactivity was almost exclusively due to the parent drug in all animal species studied, as well as in man. The metabolism of levocabastine in man was very similar to that in rabbits and dogs; the ester glucuronidation and subsequent deglucuronidation were the only metabolic pathways that could be detected in these species. A metabolism and excretion study in man indicated that about 70% of an oral dose of levocabastine was excreted in the urine as unchanged drug. The acylglucuronide of levocabastine was the main metabolite in the urine, representing about 10% of the dose. In all species tested, unchanged levocabastine was the main component of the urinary and fecal excretion.

After oral administration of ³H-levocabastine, the radioactivity was excreted rapidly (73-83% of the dose within 24 hours) in most animal species studied. At 96 hours after oral dosing, the excretion was

almost complete in mice, rabbits, dogs and female rats, but not in male rats, due to a more extensive enterohepatic circulation of metabolites. In rabbits, mice and male rats, the fractions of the radioactivity excreted in the urine were similar to those in the feces. In female rats, there was a predominant excretion in the urine, whereas in dogs the excretion in the feces was more than twice that in urine. In man, the excretion was slower than in the animal species and amounted to 54% in the urine and 12% in the feces within 4 days.

The effects of renal insufficiency on the pharmacokinetics of orally administered levocabastine were examined in non-dialysis patients and patients undergoing regular hemodialysis. In relation to healthy volunteers, these patients demonstrated impaired oral absorption of levocabastine, reduced urinary excretion of the unchanged drug, and a prolonged half-life (from 36 hours to 95 hours) and overall exposure to levocabastine based on AUC was increased by 56%. Although a 6-hour hemodialysis procedure starting 4 hours post-dosing eliminated 10% of the oral dose, the terminal half-life and the total area under the plasma concentration-time curve did not differ significantly between the hemodialysis and the non-hemodialysis patients.

In humans, the plasma protein binding of levocabastine was pH-dependent and averaged $54.7 \pm 1.6\%$ at plasma concentrations of 10 ng/mL. The plasma protein binding increased with pH, resulting in 40% at pH 7.0, 55% at pH 7.4 and 67% at pH 7.8. Albumin was the main binding plasma protein for levocabastine in human plasma.

In vitro analysis of the plasma protein binding of levocabastine showed no alteration by imipramine, propranolol, diphenylhydantoin, diazepam, cimetidine, indomethacin and ketoconazole. In the presence of high concentrations of sulfamethazine, tolbutamide and warfarin, the unbound fraction of levocabastine increased slightly; however, these changes were minor and not clinically relevant for a drug which is 55% bound. At a high levocabastine concentration of 50 ng/mL, there was no change in the plasma protein binding of imipramine ($89.1 \pm 1.4\%$), propranolol ($85.3 \pm 1.2\%$), diphenylhydantoin ($85.5 \pm 1.2\%$), warfarin ($97.3 \pm 0.3\%$), ketoconazole ($98.3 \pm 0.1\%$) and diazepam ($98.5 \pm 0.1\%$).

Interaction studies were performed in healthy volunteers to evaluate the simultaneous nasal application of levocabastine and oxymetazoline. Oxymetazoline may transiently reduce the nasal

absorption of levocabastine into the systemic circulation. After repetitive simultaneous application, however, levocabastine absorption was no longer influenced by the decongestant.

Co-administration of the CYP3A4 inhibitors ketoconazole or erythromycin had no impact on the pharmacokinetics of intranasal levocabastine. Intranasal levocabastine did not change the pharmacokinetics of loratadine.

In addition to the subjective assessments performed during clinical trials, the possible central effects of levocabastine nasal spray were investigated in specially-designed psychoperformance studies.

In one study, the combination of the nasal spray with diazepam failed to reveal any consistent effects on psychomotor performance. When 0.8 g/kg of alcohol was given in combination with the nasal spray at steady-state, the only significant change in the EEG was an increase in theta wave. In objective psychometric tests, a slight reduction in accuracy was observed, while reaction times remained unaltered. It was concluded that when given on a t.i.d. basis, there is no evidence of central effects of levocabastine nasal spray; when combined with alcohol a slight interaction seems possible, and when given in combination with diazepam, no potentializing effects can be expected.

A second study conducted under double-blind placebo-controlled conditions was designed to allow separation of the "pure" alcohol effect from effects resulting from the interaction of alcohol with levocabastine. Levocabastine was provided at doses of 2 puffs t.i.d., (0.5mg/mL) over a period of 10 days (to ensure steady-state), whilst alcohol was provided at a dose of 0.7g/kg; this was consumed following a baseline measurement of psychomotor performance. Additionally, the effects of acute administration of levocabastine on psychomotor performance were established following the first dose. Psychomotor tests exploring cognitive vigilance, memory, and reaction times were performed. The deleterious nature of ethanol was evident on psychomotor performance in all tests, but no effects attributable to levocabastine were observed. The report concluded that there was no evidence of a psychomotor interaction between levocabastine and alcohol.

TOXICOLOGY

Acute Toxicity

Only in the dogs was there sufficient mortality to permit calculation of LD₅₀ (Table 4). No large differences between sexes or species were observed. At very high dose levels after oral administration (1,280 mg/kg) effects were mainly of a CNS nature, such as peripheral ptosis, sedation and transient decrease in activity. A dermal application of 2 g/kg (the maximally applicable dose) did not result in any adverse effects in rabbits. No specific drug-related effects were noted at necropsy in any animal species.

In an inhalation study which exposed rats to 1 g/m³ levocabastine for 4 hours, the only finding was a transient decrease of general activity. No drug-related effects were observed at necropsy.

Table 4: Single dose toxicity studies of levocabastine

Animals	Route of Administration	Formulation	No. Animals	LD ₅₀ 14 days
Single dose pilot toxicity studies:				
mouse	oral	suspension 0.5 mg/mL	10 M 10 F	> 25 mg/kg
	i.v.	solution 0.5 mg/mL	10 M 10 F	>0.5 mg/mouse
	i.v.	solution 2.5 mg/mL	5 M 5 F	>2.5 mg/mouse
rat	oral	suspension 0.5 mg/mL	10 M 10 F	> 22 mg/kg
	i.v.	solution 0.5 mg/mL	10 M 10 F	> 2 mg/rat
	i.v.	solution 2.5 mg/mL	5 M 5 F	> 10 mg/rat
dog	oral	suspension 0.5 mg/mL	2 M 2 F	> 4.5 mg/kg
	i.v.	solution 0.5 mg/mL	4 M 4 F	> 25 mg/dog
	i.v.	solution 2.5 mg/mL	2 M 2 F	>125 mg/dog
Single dose toxicity studies:				
mouse	oral	suspension 0.5 mg/mL	10 M 10 F	> 2560 mg/kg
rat	oral	suspension 0.5 mg/mL	10 M 10 F	> 2560 mg/kg
	inhalation	crystalline powder	5 M 5 F	> 1 g/m ³ for 4 hours
rabbit	abraded skin	crystalline powder	5 M 5 F	> 2 g/kg
	unabraded skin	crystalline powder	5 M 5 F	> 2 g/kg
dog	oral	suspension 0.5 mg/mL	4 M 4 F	≈ 2560 mg/kg

Chronic Toxicity

Table 5 summarizes the chronic toxicity studies carried out in various animal species. Following oral administration in Wistar rats, 10 mg/kg was found to be non-toxic in the 3-month study and 2.5 mg/kg in the 6-month study, whereas following intravenous administration the non-toxic doses were 0.05 and 0.10 mg/kg. In Beagle dogs, 5 mg/kg was non-toxic in the 3-month and the 12-month studies and 20 mg/kg was non-toxic in the 3-month study only. Following intravenous administration, 0.05, 0.1 and 0.20 mg/kg were non-toxic in Beagle dogs.

Clinical signs of a CNS type (ptosis, pilo-erection) and the death of two males were seen in rats dosed at 160 mg/kg/day (approximately 10000 x maximum nasal human use level) (Table 5). CNS effects (decreased general activity) also occurred in dogs dosed at 80 mg/kg (approximately 5000 x maximum nasal human use level) for 12 months, and to a lesser extent at 20 mg/kg (approximately 1200 x maximum nasal human use level). No specific drug-related ophthalmic abnormalities were found in any study. The oral administration of levocabastine reduced body weight in rats at 10 mg/kg (in the 6-month study only), 40 and 160 mg/kg/day and in dogs at 20 and 80 mg/kg/day in the 12-month study.

Some hematological changes were observed, but they were all within or at the borderline of the normal range. In the 12-month dog study, dosing at 80 mg/kg and to a lesser extent at 20 mg/kg, resulted in increased haptoglobin and decreased cholesterol and albumin. Some other serum parameters (increase of alkaline phosphatase and inorganic phosphate) changed during the last part of this study, but the values were still within normal limits. No specific disturbances in the urine parameters were observed except for a decrease of pH (males) and creatinine, and the presence of RBC and fatty epithelial cells in the sediment of rats dosed at 160 mg/kg. In most oral studies, a tendency to increased adrenal fat with a higher weight of adrenals was found. In rats, at the highest toxic dose level of 160 mg/kg, kidney changes, mammary gland stimulation (also observed at 40 mg/kg in the 3-month study), a more resting aspect of the genital tract in females and degeneration of testicular germinal epithelium in males were the most important histological changes. In some dogs, decreased secretory activity of the prostate was found at 80 mg/kg (12-month study).

In the intravenous toxicity studies and the dermal study, no specific drug-related changes were observed except for slightly decreased body weight in male rats dosed at 0.20 mg/kg (12 x maximum nasal human use level).

Table 5: Summary of chronic toxicity

SPECIES	ROUTE OF ADMINISTRATION	NO. AND SEX OF ANIMALS/GROUP	DOSE (mg/100g feed)	DOSE (mg/kg) ^a		DURATION OF TREATMENT	OBSERVATIONS
				male	female		
Wistar Rats	Oral	20 M 20 F	10, 40, 160	9.0 36.0 145.1	10.0 41.1 172.7	3-Month	-at 10 mg/kg: no adverse effects; -at 40 and 160 mg/kg: decreased food consumption and body weight gain, mammary gland stimulation and increased adrenal fat in the zona glomerulosa and fasciculata; increase in urobilinogen (F); -at 160 mg/kg: increased segmented heterophils, decreased hematocrit, hemoglobin, RBC, lymphocytes, serum protein levels (within normal range); urinalysis: decrease of creatinine, pH (M); tissue changes: enlarged adrenals and ovaries (F) -medulla of the kidneys was swollen with desquamation of epithelial cells; -degeneration of testicular germinal epithelium and reduced spermatogenesis; -reduced cyclic activity in the genital tract (F).
	i.v.	20 M 20 F	0.05, 0.10, 0.20			1-Month	-at 0.20 mg/kg decrease in food consumption and body weight gain in M.
Fisher Rats	Oral	20 M 20 F	2.5, 10, 40	1.6 6.4 27.0	2.3 9.0 38.8	6-Month	-2.5 mg/kg: decrease in body weight; -10 mg/kg: decreased body weight, hematological changes (within normal range), increased weight of adrenals; -40 mg/kg: same as for 10 mg/kg but more pronounced; waste of food increased in F.
Beagle Dogs	Oral	3 M 3 F	5, 20 and 80			3-Month	-no adverse effects at 5 and 20 mg/kg; -increased fat in adrenals and increased body weight gain at 80 mg/kg.
		4 M 4 F	5, 20 and 80			12-Month	-5 mg/kg: no adverse effects; -20 mg/kg: transient decrease in general activity; increased alkaline phosphatase in last 6 months (within normal range); increase liver weight and body weight; -80 mg/kg: same as 20 mg/kg and also: permanent decrease in general activity with decubitus; transient increase in both WBC and band neutrophils (within normal range); transient increase in inorganic phosphate (within normal range); terminal increase in chloride; moderate increase in spleen, pancreas and adrenal weight; increased deposition of hepatocellular pigment; decreased secretory activity in the prostate of some dogs.
Beagle Dogs	i.v.	4 M 4 F	0.05, 0.10 and 0.20			1-Month	-no adverse effects were noted.
New Zealand White Rabbits	Dermal	5 M 5 F	0.5			21-Days	-non-progressive irritation at the sites of administration.

^a Mean daily dose expressed in mg/kg body weight calculated from food consumption and body weight.

Carcinogenicity Studies

Levocabastine was orally administered to three groups of 50 male and 50 female albino Swiss mice at doses of 3.0, 12.1 and 49.0 mg/kg in males, and 3.2, 12.9 and 52.0 mg/kg in females daily for 20 months (Table 6). Dosing of females at 12.9 and 52 mg/kg (800 and 3,200 x maximum nasal human use level) resulted in a prolactin-mediated drug- and dose-related increase of pituitary gland hyperplasia and mammary gland stimulation associated with an increase of mammary gland adenocarcinoma and pituitary gland adenoma.

Levocabastine was administered to three groups of 50 male and 50 female SPF Wistar rats at doses of 1.5, 6.1 and 24 mg/kg in males and 2.0, 9.0 and 34 mg/kg in females daily for 24 months (Table 6). Overall mortality (including controls) was approximately 50% in males and 40% in females. Toxicity was observed at all dose levels by altered body weight gain, and histopathological non-neoplastic changes in the high-dose males. With regard to the incidence of neoplastic changes, it can be concluded that levocabastine up to the highest tested dose level is not carcinogenic in rats.

Table 6: Summary of carcinogenicity studies

SPECIES	ROUTE OF ADMINISTRATION	NO. AND SEX OF ANIMALS/GROUP	DOSE (mg/100g feed)	DOSE (mg/kg day)^a	DURATION OF TREATMENT	OBSERVATIONS
Albino Swiss Mice	Oral-diet	50 M 50 F	2.5, 10 and 40	3.0, 12.1, and 49.0 3.2, 12.9, and 52.0	20-Month	-increase mortality of females at high-dose; -dose-related increased incidence of subcutaneous masses in mammary gland in females; -decrease in body weight in males at high-dose; -dose-related increased incidence of mammary gland stimulation, mammary gland tissue masses and swollen pituitary glands; -decreased incidence of swollen uteri; -increase of white blood cells in high-dose.
SPF Wistar Rats	Oral-diet	50 M 50 F	2.5, 10 and 40	1.5, 6.1, and 24.0 2.0, 9.0, and 34.0	24-Month	-dose-dependent decrease body weight in males; -increased body weight in females; -increased incidence of small and soft testes in high-dose males; -increased incidence of mammary gland tissue masses in high-dose females.

^a Mean daily dose expressed in mg/kg body weight calculated from food consumption and body weight.

Mutagenicity

The mutagenic potential of levocabastine has been evaluated in four test systems: Ames reverse mutation test with *Salmonella typhimurium* (with and without enzymatic activation), sex-linked recessive lethal test in *Drosophila melanogaster*, a micronucleus test in rats and a dominant lethal test in male and female mice. No mutagenic potential was demonstrated by levocabastine at doses up to 40 mg/kg in any of these tests.

Other Tests

Dermal Sensitization in Guinea Pigs

Levocabastine was classified as having "weak" potential to induce dermal sensitization, since the sensitization rate was zero, as studied using the Magnusson maximization technique in guinea pigs.

Reproduction and Teratogenicity Studies

Segment I (fertility), II (embryotoxicity and teratogenicity) and III (peri- and postnatal) studies were conducted in rats (diet). Similarly Segment II studies using gavage were conducted in mice, rats and rabbits (Table 7).

In both Segment I and III studies, dose levels up to and including 20 mg/kg were devoid of any effect on fertility or peri- and postnatal parameters.

In the mice Segment II study, dosing at 10 and 40 mg/kg did not result in adverse effects, whereas at 160 mg/kg embryonal resorptions and teratogenic effects were increased.

In the rat Segment II studies, dose levels up to and including 20 mg/kg showed no embryotoxicity or teratogenicity, whereas 40 mg/kg (diet and gavage) was slightly teratogenic. At 160 mg/kg, maternal toxicity, teratogenicity and increase of resorptions were present.

In the rabbit Segment II study, no embryotoxic or teratogenic effects were noted up to 20 mg/kg (1200 times the recommended nasal spray dosage).

Table 7: Summary of reproduction and teratogenicity studies

SPECIES	ROUTE OF ADMINISTRATION	TYPE OF STUDY	DURATION OF STUDY	DOSE (mg/100g feed)	DOSE (mg/kg) ^a		OBSERVATIONS
					male	female	
Wistar Rats	Oral	Male and Female Fertility (Segment I)	59 days before mating in 20 M rats/group; from 14 days prior to mating throughout gestation to 20 F rats/group	0 5 10 20	4.7 ^b 9.0 18.2	5.9 ^b 13.4 28.2	Body weight decreased in male rats dosed at 20 mg/kg; an increase in the weight and food consumption of female rats dosed at 10 and 20 mg/kg. No adverse effect on the fertility of male and female rats could be detected.
Cobs CD1 Mice	Oral	Embryotoxicity and Teratogenicity (Segment II)	from day 6 to 16 of pregnancy to 30 F mice/group	0, 10, 40 and 160			No maternal, embryonal or teratogenic effects at 10 and 40 mg/kg. At 160 mg/kg, maternal toxicity, increased embryonal resorptions and slight teratogenicity (open eyelids in 15/147 mice) were observed.
Wistar Rats	Oral-via diet	Embryotoxicity and Teratogenicity (Segment II)	from day 6 to 15 of pregnancy to 20 F rats/group	0 5 10 20 40 160		5.7 11.0-11.7 ^c 23.8 45.0 143.1	Up to 20 mg/kg, no adverse effects were noted. At 40 mg/kg, slight teratogenicity was noted (polydactyly in 13/209 fetuses). At 160 mg/kg, maternal toxicity, increased embryonal resorption and increased incidence of polydactyly (34/36) and brachygnathia (12/36).

^a Mean daily dose expressed in mg/kg body weight calculated from food consumption and body weight.

^b Daily doses during pre-cohabitation period. During post-mating period (for female rats only) the daily doses were 4.9, 9.8 and 19.3.

^c The results of two studies are combined, both studies had a 10 mg/kg group.

Table 7: Summary of reproduction and teratogenicity studies (cont'd)

SPECIES	ROUTE OF ADMINISTRATION	TYPE OF STUDY	DURATION OF STUDY	DOSE (mg/100g feed)	DOSE (mg/kg) ^a		OBSERVATIONS
					male	female	
Wistar Rats	Oral-gavage	Embryotoxicity and Teratogenicity (Segment II)	from day 6 to 15 of pregnancy to 24F rats/group	0, 10, 40 and 160			At 10 mg/kg, no adverse effects were seen. At 40 mg/kg, slight teratogenic effects (polydactyly in 3/237 fetuses) were noted. At 160 mg/kg, maternal toxicity, increased embryonal resorptions and teratogenicity (polydactyly in 22/22 fetuses) were observed.
New Zealand White Rabbits	Oral-gavage	Embryotoxicity and Teratogenicity (Segment II)	from day 6 to 18 of pregnancy to 15 F rabbits/group	0, 5, 10 and 20			No adverse effects were noted on the progeny at any dose level.
Wistar Rats	Oral	Peri- and Post-natal Toxicity (Segment III)	from day 16 of gestation through a 3-week lactation period in 20 F/group	0 5 10 20		5.6 10.7 21.7	No adverse effects were noted at any of the administered doses.

^a Mean daily dose expressed in mg/kg body weight calculated from food consumption and body weight.

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PART III: CONSUMER INFORMATION

Pr LIVOSTIN®*

levocabastine Nasal Spray

0.5 mg/mL as levocabastine hydrochloride

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about LIVOSTIN®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

LIVOSTIN® is a prescription medication for the treatment of allergies in people 12 years of age and older. The nasal spray is for the rapid and long-lasting relief of nasal complaints, such as sneezing, runny and itchy nose associated with allergies to grass, pollen, moulds, dust or other substances.

What it does:

When LIVOSTIN® is sprayed into your nose, it helps reduce the symptoms associated with allergies such as sneezing, runny and itchy nose.

LIVOSTIN® blocks the action of histamine and relieves allergy symptoms. Histamine is a chemical released by the immune system - the body's defence against invading substances - when the body is affected by substances that you are allergic to (allergens).

When it should not be used:

Do not use LIVOSTIN® if you are allergic to it or any of its ingredients (see **What the nonmedicinal ingredients are**) below. If you are not sure, talk to your doctor or pharmacist.

What the medicinal ingredient is:

levocabastine hydrochloride

What the nonmedicinal ingredients are:

benzalkonium chloride, propylene glycol, polysorbate 80, disodium phosphate, monosodiumphosphate, disodium edetate, hypromellose and water.

For a full listing of nonmedicinal ingredients see the product monograph.

What dosage forms it comes in:

LIVOSTIN® comes in a nasal spray. It is a sterile white suspension in plastic spray bottles containing 15 milliliters.

WARNINGS AND PRECAUTIONS

Before you use LIVOSTIN® talk to your doctor or pharmacist if you are:

- pregnant or planning to become pregnant.
- breast-feeding.
- suffering from a kidney disorder.

Except on the advice and under the supervision of your doctor, you should not use LIVOSTIN® nasal spray if you are suffering from a kidney disorder.

LIVOSTIN® usually does not affect alertness or concentration. However, should you feel drowsy, be careful while driving or operating machinery.

LIVOSTIN® is only for use in people 12 years and older.

Your doctor has prescribed this medicine for you. Do not give this medicine to anyone else.

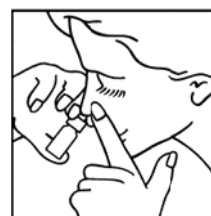
INTERACTIONS WITH THIS MEDICATION

No interactions with other medications have been reported during Clinical Trials.

PROPER USE OF THIS MEDICATION

LIVOSTIN® nasal spray comes as a suspension. So **shake the bottle well** before each use. For adults and children 12 years of age and older, the usual dose is **2 sprays of LIVOSTIN® for each nostril twice a day**. If your symptoms are very bothersome, you can spray 3 or 4 times a day. Follow your doctor's directions carefully.

1. Shake the bottle well before removing the cap.
2. Before using LIVOSTIN® nasal spray for the first time, remove the cap and squeeze the bottle once or twice until a fine spray appears in the air.
3. Blow your nose.



4. Hold the bottle as shown in the picture. Tilt your head slightly forward. Keep one nostril tightly closed and insert the nozzle into the other nostril.
5. Spray twice, while breathing in through the same nostril.
6. Repeat steps 4 and 5 for the other nostril.

Overdose:

There have been no reports of overdosage of LIVOSTIN®. If you accidentally drink LIVOSTIN®, drink plenty of non-alcoholic fluids to speed up the elimination of drug from your system and contact your doctor.

In case of accidental drug overdose, contact a health care practitioner, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss your dose by several hours, take your next dose at your usual time. **Do not** take an extra dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Undesired effects may occur while using LIVOSTIN®.

Headache is the most common unwanted effect reported with LIVOSTIN® Nasal Spray. Should you experience this or any other unwanted effect while using LIVOSTIN® Nasal Spray, including those listed below, you should inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very rare	abnormally fast heartbeats			✓
	difficulty breathing, airway constriction			✓
	Hypersensitivity			✓

Unwanted effects that have been reported very rarely with LIVOSTIN® nasal spray include nausea, fatigue, achiness, irritation, discomfort, pain, burning, or dryness at the site of application, a general feeling of being unwell, sinusitis, drowsiness, dizziness, throat pain, nose bleed, cough, stuffy nose, nasal discomfort, and swelling of the eyelid.

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

HOW TO STORE IT

LIVOSTIN® should be stored at room temperature (15°C-30°C). LIVOSTIN® nasal spray should be kept in a safe place where children cannot reach it.

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 0701D
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available in the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, 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 at: <http://www.janssen.ca> or by contacting the sponsor, Janssen Inc., at: 1-800-567-3331

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