

PRESCRIBING INFORMATION

ELTOR® 120

(Pseudoephedrine Hydrochloride)
Manufacturer's Standard

Nasal decongestant, Sympathomimetic and Bronchodilator

sanofi-aventis Canada Inc.
2905 Place Louis-R-Renaud
Laval, Quebec H7V 0A3

Date of Revision:
February 7, 2019

Submission Control No.: 239637

s-a Version 5.0 dated February 7, 2019

NAME OF DRUG:

ELTOR[®] 120

(Sustained-release pseudoephedrine hydrochloride)

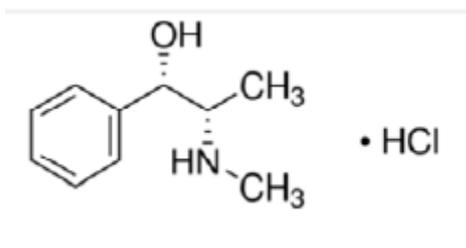
THERAPEUTIC CLASSIFICATION

Nasal decongestant, sympathomimetic and bronchodilator

STRUCTURAL FORMULA AND CHEMISTRY

(+)-Pseudoephedrine Hydrochloride

Structural Formula



Molecular Formula C₁₀H₁₅NO.HCl

Molecular weight 201.69

Chemical Name (+)-*threo*-α[1-(methylamino)ethyl]benzyl alcohol hydrochloride.

Description A fine white to off-white powder or crystals with a faint characteristic odour, soluble in water, in alcohol, and in chloroform. It has a melting range of 181°C to 186°C.

ACTION

Pseudoephedrine has been shown to have a similar action on the human nasal mucosa to ephedrine.² It is an effective nasal decongestant and bronchodilator. Decongestion of the nasal mucosa occurs through vasoconstriction, and the relief of obstructed air passages by a direct action on the smooth muscle of the bronchi. The vasopressor effect of pseudoephedrine is less than that of ephedrine.

INDICATIONS - CLINICAL USES

ELTOR[®] 120 is indicated for conditions of acute coryza, sinusitis, and vasomotor or allergic rhinitis, by providing temporary nasal and sinus decongestion. It may also be used as an adjunct to antibiotics, antihistamines, analgesics and antitussives in the treatment of the above conditions.

CONTRAINDICATIONS

ELTOR 120 is contraindicated in patients receiving or having received MAO inhibitors in the preceding three weeks, and in patients with known hypersensitivity to the pressor amines.

PRECAUTIONS

ELTOR 120 should be used with caution in hypertensive and diabetic patients; patients with latent or clinically recognized open angle glaucoma; patients with coronary artery disease; patients with congestive heart failure; patients with prostatic hypertrophy; hyperthyroid patients and patients with urinary retention.

INTERACTIONS

Concomitant use of pseudoephedrine with betablockers may reduce the antihypertensive effect of betablockers.

ADVERSE REACTIONS

Adverse effects are uncommon with ELTOR 120, and mainly of a subjective nature. Headache, dizziness, insomnia, tremor, confusion, CNS stimulation, muscular weakness, dry mouth, nausea, vomiting, difficulty in micturition, urinary retention, palpitations, tightness in the chest, syncope, and ischemic colitis, tachycardia, acute generalized exanthematous pustulosis (AGEP), and manic symptoms (such as insomnia, high or irritable mood, inflated self-esteem, increased activity or restlessness, racing thoughts, talking fast, and distractibility) have been encountered.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Increase in pulse and respiratory rate, signs of central nervous system stimulation, disorientation, headache, dryness of the mouth, nausea and vomiting.

Treatment

Gastric lavage, repeated, if necessary. Acidify the urine and institute general supportive measures. If CNS excitement is prominent, a short-acting barbiturate may be used.

PHARMACOLOGY

Animal

Early investigators,² noting pseudoephedrine's action on human nasal mucous membrane, tested the side effects of the drug in a variety of species. The production of mydriasis was shown to be less prominent with pseudoephedrine than with l-ephedrine. In decerebrated pithed cats, 2 mg of ephedrine raised carotid blood pressure 57 MM Hg whereas the maximum rise with the same dose of pseudoephedrine was 41 MM Hg. Intravenous injections of from 0.5 to 2 mg/kg pseudoephedrine into anesthetized dogs produced increases in blood pressure and decreases in cardiac contractility.³ The same investigators found that as an oral diuretic in the rat, d-pseudoephedrine was 50% less effective than d-ephedrine. l-ephedrine was inactive as a diuretic.

In the anesthetized dog, Patil *et al.*,⁴ found that pseudoephedrine possessed only 20% of the relative pressor potency of ephedrine although the duration of blood pressure elevation was approximately doubled. An increase in heart rate paralleled these blood pressure effects. The rate of development of tachyphylaxis to the pressor effect was found to be greater with pseudoephedrine than with ephedrine.

Aviado *et al.*,⁵ demonstrated significant bronchodilator action in the dog locally via bronchial arterial injections of 5 mg pseudoephedrine. No systemic change was observed with small doses. Intravenously, 0.5 to 1.0 mg/kg pseudoephedrine elicited hypertension along with measurable bradycardia and a reflex increase in vagal tone. Blood flow responses were biphasic: an initial increase in flow concomitant with the rise in blood pressure followed by a reduction in flow in most vascular beds. The vertebral artery, however, usually exhibited vasodilation with pseudoephedrine. In general, it should be noted that the vascular side effects due to pseudoephedrine were weaker in nature than with ephedrine.

Clinical

Pseudoephedrine is a sympathomimetic agent which possesses both direct and indirect adrenergic properties. It is well absorbed in the G.I. tract. The plasma half -life of the drug is shortened when the urinary pH is lowered.

In a study⁶ using maximal nasal inspiratory flow rate as a test of nasal decongestion, ten patients with vasomotor rhinitis were given 60 mg oral pseudoephedrine. A statistically significant

increase in nasal air flow was observed in comparison to an oral lactose placebo. The objective improvement with pseudoephedrine was comparable to the effect obtained 10 minutes after instillation of a 1% ephedrine into each nostril. Subjectively, six of the ten patients felt less nasal stuffiness after pseudoephedrine.

Pseudoephedrine's action on systolic blood pressure has been investigated.⁷ In general, the rise in pressure after 150 mg pseudoephedrine orally administered did not reach the magnitude nor duration as the same dose of ephedrine. Side effects were not observed with pseudoephedrine, but palpitations, tremors, and emesis were seen after ephedrine.

A comparison of the serum pseudoephedrine levels following a single oral dose of ELTOR 120 (120 mg sustained-release pseudoephedrine) with two oral doses of 60 mg pseudoephedrine, in an immediate-release form given at six-hour intervals, showed that at one hour, the serum pseudoephedrine level produced by the two preparations was similar. At six hours, however, the mean pseudoephedrine level, following the immediate-release form was lower (135 ng/mL) than with the sustained-release form (240 ng/mL).

A determination of serum levels of pseudoephedrine during a six day period of twice a day dosing with ELTOR 120 (120 mg sustained-release pseudoephedrine) has been conducted.⁸ An average plateau concentration of about 380 ng/mL was reached within two days. This level fluctuated between a mean low of 250 ng/mL and a mean high of 500 ng/mL during the remainder of the six day experiment. Sporadic elevations yielding values between 600 ng/mL and 672 ng/mL were recorded in five instances in the test group.

Two placebo controlled double blind studies⁸ have been conducted on a total of 198 "common cold" patients, to objectively determine the effectiveness of two doses of pseudoephedrine 60 mg, taken six hours apart, and a single dose of ELTOR 120 (120 mg sustained-release pseudoephedrine) through measurements of nasal airway resistance. Statistical analysis of nasal airway resistance values accumulated for each treatment group showed both a single dose of ELTOR 120 and repeated doses of immediate-release pseudoephedrine 60 mg produced a highly significant decongestant effect over a twelve hour period when compared with placebo.

Mild and expected side effects were reported among the three treatment groups. However, there were no reports of serious side effects or adverse reactions, nor were there any clinically significant changes in blood pressure and pulse measurements.

TOXICOLOGY

Animal

The intravenous LD₅₀ in mice was found to be approximately 88-89 mg/kg.⁴ Intravenously, the minimum lethal dose (MLD) of pseudoephedrine in rabbits is 75 mg/kg compared to 60 mg/kg for ephedrine.² Subcutaneously, the MLD for pseudoephedrine in that species is 500 mg/kg.¹

Immediate-release capsules of pseudoephedrine were compared in the dog with ELTOR 120 (120 mg sustained-release pseudoephedrine).⁸ The oral MLD for the immediate-release material was observed to be approximately 200 mg/kg while that of the sustained-release preparation was

approximately 510 mg/kg. Mydriasis, muscle tremors, hyperactivity, head jerk, loss of the righting reflex and death were elicited with both forms at these dosages.

Necropsy revealed similar gross lesions in all dogs that died, consisting of marked hepatic and renal congestion and hemorrhages in the myocardium.

Subacute oral toxicity studies were performed in Beagle dogs for a period of 39 days and in mongrel dogs for 30 days. Treatment rates of 0, 10, 25 and 50 mg/kg/day were used for both ELTOR 120 and an immediate-release pseudoephedrine animals being dosed once daily with ELTOR 120 and twice daily with the latter formulation. Initially, dose levels of 100 mg/kg/day were also used, but at this rate a death occurred in each treatment group within the first two days of treatment, and this dose level was discontinued.

Clinical signs were similar in all dogs with dose-level related degrees of anxiety, mydriasis, polypnea, hyperactivity, cyanosis, convulsions and paresis of rear quarters. Food consumption and body weight decreased in a dose-response relationship with the greater decreases being produced by the immediate-release form. Hemoglobin and packed cell volume decreases were slight to moderate at all treatment levels with both drugs, while clinical chemistry and urinalysis results were unaffected by treatment.

In addition, subacute (30 days) oral toxicity studies⁸ of ELTOR 120 have been performed in New Zealand White Rabbits with daily oral mean doses of 0, 40, 100, or 160.5 mg/kg being administered of the controlled-release formulation of d-pseudoephedrine hydrochloride. Treatment with 160.5 mg/kg/day but not with 40 or 100 mg/kg/day of ELTOR 120 produced variable mydriasis in all rabbits, restlessness in some animals and self-mutilation of the skin due to apparent hyperesthesia in one rabbit. Treatment with the high dose level also had a slight detrimental effect on body weight.

Focal hepatic necrosis was noted in two high dose animals. No deaths occurred as a result of treatments. Results indicate that oral dose levels of 40 or 100 mg/kg/day of ELTOR 120 are "no effect" treatment levels in the rabbit.

Clinical

Human tolerance studies of ten days duration have been conducted on a double-blind basis to compare the tolerance of repeated doses (b.i.d.) of ELTOR 120 with repeated doses (q.i.d.) of an immediate-release preparation of pseudoephedrine HCl 60 mg and placebo.⁸ Abnormal laboratory findings (sporadic elevations of SGOT, SGPT, and SUA) were recorded in all groups, but were found to be normal on post-study follow-up, twenty-nine days later. It was concluded after reviewing and laboratory results, clinical observations and reported side effects, that both pseudoephedrine preparations were equally well tolerated and accepted by the patients.

DOSAGE AND ADMINISTRATION

Adults and children over 12 years of age: one caplet orally, every 12 hours as directed by a physician. Avoid use for prolonged periods of time except on the advice of a physician. Do not exceed recommended dosage.

STORAGE AND STABILITY

Store between 15 and 30°C.

DOSAGE FORM

Each white caplet engraved "ELTOR" on one side contains pseudoephedrine hydrochloride 120 mg and provides a continuous release of the active therapeutic agent over a 12-hour period.

Non-medicinal ingredients: Hypromellose, magnesium stearate, methylcellulose, silicon dioxide, sucrose.

Available in blister packages of 12 and 24 caplets.

BIBLIOGRAPHY

1. The Merck Index, 8th Edition, Merck & Co., Rahway, New Jersey, 1968.
2. Chen, K.K., Wee, Chang-Keng and Henriksen, Erle, Relationship Between the Pharmacological Action and the Chemical Constitution and Configuration of the Optical Isomers of Ephedrine and Related Compounds, *J. Pharm. Exptl. Therap.* 36:363-400, 1929.
3. Light, A.E., Wnuck, A.L. and deBeer, E.J., Vascular and Renal Effects of d- and l-Ephedrine and d- and l-Pseudoephedrine, *Fed. Proc.* 18:915, 1959.
4. Patil, Popat N., Tye, A. and LaPidus, J.B., A Pharmacological Study of the Ephedrine Isomers, *J. Pharm. Exptl. Therap.* 148:158-168, 1965.
5. Aviado, D.M., Jr., and Wnuck, A.L. and deBeer, E.J., Cardiovascular Effects of Sympathomimetic Bronchodilators: Epinephrine, Ephedrine, Pseudoephedrine, Isoproterenol, Methoxyphenamine and Isoprophenamine, *J. Pharm. Exptl. Therap.* 122:406-417, 1958.
6. Benson, M.K., Maximal Nasal Inspiration Flow Rate: Its Use in Assessing the Effect of Pseudoephedrine in Vasomotor Rhinitis, *Europ. J. Clin. Pharm.* 3:182-184, 1971.
7. Chen, x.K., A Comparative Study of Ephedrine, Pseudoephedrine and B-phenylethylamine, *Archiv. International Med.* 39:404-411, 1972.
8. Data on file, Merrell Dow Pharmaceuticals (Canada) Inc., Richmond Hill, Ontario, 1973.