

PRODUCT MONOGRAPH

RHINARIS-CS ANTI-ALLERGIC NASAL MIST

Cromolyn Sodium Nasal Solution USP
2% w/v

Nasal Metered-Dose Mist

Prevention of Seasonal Allergic Rhinitis

PENDOPHARM, Division of Pharmascience Inc.

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Date of Revision:

April 24, 2013

Control # 163420

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THERAPEUTIC CLASSIFICATION

Prevention of Seasonal Allergic Rhinitis

ACTION AND CLINICAL PHARMACOLOGY

In vitro and in vivo animal studies have shown that Cromolyn Sodium (Sodium Cromoglycate) inhibits the degranulation of sensitized mast cells occurring after exposure to specific antigens. Cromolyn Sodium acts by inhibiting the release of mediators from mast cells. Studies show that Cromolyn Sodium indirectly blocks calcium ions from entering the mast cell, thereby preventing mediator release.

Cromolyn Sodium has no intrinsic bronchodilator, antihistaminic or anti-inflammatory activity. It reduces the symptoms of seasonal rhinitis by blocking the release of histamine and other mediators of immunity rather than blocking H1-histamine receptors.

Cromolyn Sodium is poorly absorbed from the gastrointestinal tract but is rapidly absorbed following inhalation or intranasal administration. Once absorbed Cromolyn Sodium is rapidly cleared by the liver and kidneys prior to excretion in the bile and urine. Apart from the liver and kidneys there is no significant accumulation in any tissues.

Cromolyn Sodium is not metabolized and is excreted unchanged.

INDICATIONS AND CLINICAL USE

RHINARIS-CS ANTI-ALLERGIC NASAL MIST is indicated for the relief of the nasal symptoms of seasonal allergic rhinitis, such as congestion (stuffy nose), sneezing and itchy, runny nose.

CONTRAINDICATIONS

RHINARIS-CS ANTI-ALLERGIC NASAL MIST is contraindicated in those patients who have shown hypersensitivity to ingredients listed under COMPOSITION section.

WARNINGS

1. Patients should be instructed that if they do not obtain relief of their symptoms within 7 days of starting treatment, a doctor should be consulted.
2. Patients with nasal polyps should not use this product except on the advice of a doctor.
3. Patients who are pregnant or nursing a baby should consult a doctor prior to use.

PRECAUTIONS

Safety and effectiveness in children below the age of 5 have not been established.

ADVERSE REACTIONS

Slight irritation of the nasal mucosa may occasionally occur. Cases of erythema, urticaria or maculo-papular rash have been reported but these have resolved within a few days of drug withdrawal. Headache, sneezing, cough and unpleasant taste in the mouth have also been reported to occur occasionally. Eosinophilic pneumonia has been reported rarely. Possible immunologic changes resulting in reactions such as polymyositis, pneumonitis and heart failure, urticaria and anaphylaxis have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been no known cases of overdosage with Cromolyn Sodium nasal solution. Should overdosage occur symptomatic treatment is suggested.

DOSAGE AND ADMINISTRATION

Metered Dose Mist

- ▶ *Adults & children over 5 years:* One metered dose spray into each nostril 6 times daily (single dose 2.6 mg, total daily dose 15.6 mg cromolyn sodium). When adequate response has been obtained, dosage should be reduced to 2–3 times per day (every 8–12 hours per day).
- ▶ To help maintain relief, it is important to continue treatment throughout the allergy season, even when the patient is free of symptoms.
- ▶ The recommended dose should not be exceeded.
- ▶ Due to the slow onset of action of this medication, other allergy medications may be used as required during the first week of therapy.

- ▶ For consumer product information and specific directions on use of the metered dose spray, see INFORMATION FOR THE CONSUMER.

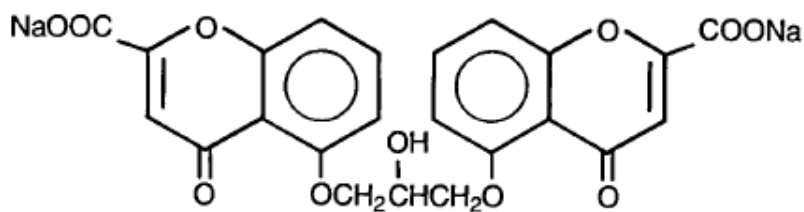
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Cromolyn Sodium (Sodium Cromoglycate)

Chemical Name: 4H-1-Benzopyran-2-carboxylic acid, 5,5'-[(2-hydroxy-1,3-propanediyl)bis(oxy)]bis[4-oxo-, disodium salt]

Structural Formula:



Molecular Formula: C₂₃H₁₄Na₂O₁₁

Molecular Weight: 512.3

Description: An odourless, white, hydrated crystalline powder. It is freely soluble in water up to 5 percent at 20°C. It is insoluble in alcohol and sparingly soluble in common organic solvents such as dioxan, pyridine, ether and chloroform.

Composition

RHINARIS-CS ANTI-ALLERGIC NASAL MIST (Cromolyn Sodium Nasal Solution USP) is a 2% (w/v) solution of Cromolyn Sodium USP in purified water. Also contains disodium EDTA 0.01% and benzalkonium chloride 0.01% as a preservative.

Storage Recommendations

Store between 15° and 30°C. Protect from direct sunlight.

AVAILABILITY OF DOSAGE FORMS

RHINARIS-CS ANTI-ALLERGIC NASAL MIST (Cromolyn Sodium Nasal Solution USP) 2% (w/v) is supplied in high density polyethylene bottles of either 13 mL or 26 mL, with a metered dose pump attached to the bottle.

The metered dose pump delivers approximately 0.13 mL of the 2% (w/v) solution or 2.6 mg of Cromolyn Sodium per spray mist.

INFORMATION FOR THE CONSUMER

RHINARIS-CS ANTI-ALLERGIC NASAL MIST ANTI-ALLERGIC NASAL METERED DOSE MIST (CROMOLYN SODIUM NASAL SOLUTION USP) 2% w/v

RHINARIS-CS ANTI-ALLERGIC NASAL MIST is a nonprescription drug intended to be used for the prevention and relief of the nasal symptoms of seasonal allergic rhinitis, such as congestion (stuffy nose), sneezing and itchy, runny nose. Please read the following information carefully as it will guide you in the safe use of this medication. If you are not sure what is causing your nasal symptoms, consult your doctor.

What is *seasonal allergic rhinitis*?

If your nasal passages are congested (stuffy) and you have an itchy, runny nose, you may be suffering from seasonal allergic rhinitis. This type of allergy is most often caused on a seasonal basis by exposure to airborne substances such as pollen, grasses, weeds, dust and animal dander.

What is RHINARIS-CS ANTI-ALLERGIC NASAL MIST, and how does it work?

During an allergic reaction, various substances are released by certain cells in your nose. These are called mast cells. The substances released by these cells affect your nasal passages in different ways, causing congestion, sneezing, and an itchy, runny nose. RHINARIS-CS ANTI-ALLERGIC NASAL MIST acts on the mast cells to prevent them from releasing the substances that cause these problems.

How you should take RHINARIS-CS ANTI-ALLERGIC NASAL MIST to make it work best for you:

Dosage

- ▶ *Adults & children over 5 years:* One metered dose spray into each nostril 6 times a day (single dose 2.6 mg, total daily dose 15.6 mg Cromolyn Sodium). When adequate response has been obtained, dosage should be reduced to 2–3 times per day (every 8 to 12 hours). Treatment should not be discontinued abruptly but dosage should be reduced gradually over a period of one week.
- ▶ RHINARIS-CS ANTI-ALLERGIC NASAL MIST works best at preventing your nasal allergy symptoms if you begin using it one week before contact with the cause of your allergies.
- ▶ To help maintain relief, it is important to continue treatment throughout the allergy season, even when you feel your symptoms have subsided.
- ▶ Do not exceed the recommended dose.

- ▶ Due to the slow onset of action of this medication (i.e. may take days for this medication to work), other allergy medications may be used as required during the first week of therapy.

Directions for Use

1. Remove the dust cap from the pump.
2. To actuate pump, press bottle upwards, with thumb as shown in the diagram. Repeat until one full mist is delivered.



3. Holding the bottle upright, insert the tip of the nose piece into the nostril and press the bottle fully upwards with the thumb to deliver one dose. Release and repeat the same procedure for the other nostril.



4. Wipe the nose piece and replace the dust cap after each use.

Warnings:

1. If you do not obtain relief of your symptoms within 7 days of starting treatment, consult your doctor.
2. Patients with nasal polyps should not use this product except on the advice of a doctor.
3. If you are pregnant or nursing a baby, consult your doctor prior to use.

What you should remember before taking this medication:

Remember that RHINARIS-CS ANTI-ALLERGIC NASAL MIST is used for the prevention of the symptoms caused by seasonal allergies. It is therefore important to start treatment before exposure to substances that cause your allergies, and to continue your treatment even when you are free of symptoms. If you are not sure when to start taking RHINARIS-CS ANTI-ALLERGIC NASAL MIST, consult your doctor. Keep this leaflet for future reference.

To store this medicine:

- ▶ Keep out of reach of children.
- ▶ Store between 15° and 30°C. Protect from direct sunlight.
- ▶ Contains benzalkonium chloride as a preservative.

PHARMACOLOGY

Animal Studies

Cromolyn Sodium appears to act mainly through a local effect on the lung mucosa, nasal mucosa, and eyes.

Cromolyn Sodium prevents release of the mediators of type I allergic reactions, including histamine and slow-reacting substance of anaphylaxis (SRS-A), from sensitized mast cells, initiated by the interaction of antigen with reagin antibodies.

When Cromolyn Sodium was administered intradermally with human reagin serum to macaque monkeys (*Macaca arctoides*) previously sensitized to the antigen, the compound inhibited the passive cutaneous anaphylactic (PCA) reactions.

In other macaque monkeys, Cromolyn Sodium did not inhibit the PCA skin reactions when administered intradermally with either histamine, bradykinin, or 5-hydroxy-tryptamine. Using anaesthetised marmosets (*Hapale jacchus*), passively sensitized with human reagin serum, Cromolyn Sodium was able to substantially inhibit the antigen-induced histamine bronchoconstriction after antigen challenge.

Cromolyn Sodium effectively and completely inhibits the homologous PCA reactions with reagin-like antibody in rats using egg albumin/*B. pertussis* and *N. brasiliensis* sensitized systems.

Examination of the PCA sites revealed that a rapid mast cell degranulation was a feature of reagin-induced PCA reactions which was markedly inhibited by Cromolyn Sodium. This interference with mast cell permeability was not unspecific since Cromolyn Sodium did not prevent the skin reactions or mast cell disruption produced by compound 48/80, a potent histamine releaser.

In contrast, homologous PCA reactions with precipitating antibody in guinea pigs were unaffected by Cromolyn Sodium. The drug also failed to provide any protective activity against either aerosol or intravenous antigen induced bronchospasm.

Furthermore Cromolyn Sodium did not have any effect on the release of histamine or slow-reacting substance -A(SRS-A) from actively or passively sensitized guinea-pig in vitro chopped lung when challenged with antigen.

In vitro studies

In a series of experiments using the isolated ileum of the guinea-pig, Cromolyn Sodium had no antagonistic effect against the following spasmogens, SRS-A, bradykinin, substance P, nicotine, acetylcholine, serotonin (5-HT), and histamine.

Histamine and SRS-A release from fresh human chopped lung passively sensitized with human reagin serum was measured after in vitro exposure to specific antigens.

Cromolyn Sodium, over a narrow range of concentrations, inhibited the release of both SRS-A and histamine.

In vitro, Cromolyn Sodium had no direct action on human bronchial chain nor did it have any antagonistic effect towards the response to acetylcholine, prostaglandin F₂, SRS-A and histamine.

The results of these studies indicate that Cromolyn Sodium interferes with the release of the spasmogens rather than antagonize them following their release.

Furthermore, the studies emphasize that Cromolyn Sodium is most effective prior to the antigen challenge.

Other Studies:

Cromolyn Sodium has few pharmacological effects. It is neither a bronchodilator nor an anti-inflammatory agent and its action is distinct from that of corticosteroids. Large doses of Cromolyn Sodium had negative or only weak inconsistent effects on the respiratory or cardiovascular systems of the rat, cat, guinea-pig and pig. However in the marmoset and dog there were marked effects.

In anaesthetized marmosets, Cromolyn Sodium produced a large rise in blood pressure and heart rate with doses of 20 µg/kg and above; with higher doses there was also transient apnoea. These effects were caused by stimulation of the post-ganglionic sympathetic fibers. In the marmoset Cromolyn Sodium showed no significant effect in several anti-inflammatory tests.

The effects of Cromolyn Sodium in the conscious and anaesthetised dogs are similar, and result from activation, by Cromolyn Sodium, of chemoreceptors situated in the pulmonary and coronary circulation initiating a reflex response. The reflex, mediated via vagal afferents, produces general stimulation of the para-sympathetic system producing bradycardia hypotension, bradypnoea and sometimes apnoea.

In experiments on cat trachea *in vivo*, and on isolated frog oesophagus and human bronchial epithelium *in vitro*, Cromolyn Sodium at high concentrations did not interfere with pulmonary clearance. Cromolyn Sodium does not affect steroid metabolism as indicated by plasma corticosterone and adrenal ascorbic acid levels.

Absorption, Distribution, and Excretion

Studies have been made on the distribution, metabolism, and excretion of Cromolyn Sodium in the mouse, rat, guinea-pig, rabbit, cat, dog, monkey (*Macaca speciosa*) and man.

The drug was administered by the intravenous, oral and nasal(rat) routes, as well as by inhalation. Tritium (³H) labelled Cromolyn Sodium has been used for the animal studies, whereas ¹⁴C labelled drug, radioimmunoassay, HPLC, and spectrophometric methods have been used in human studies.

Inhalation Studies

After administration of Cromolyn Sodium as a fine powder aerosol into the lungs of rats, rabbits and monkeys, all animals showed rapid clearance of the drug from the lungs.

The rate of absorption was such that 75% of the inhaled dose had been removed in 2 hours and after 24 hours less than 2% of the inhaled dose remained following absorption. Only the liver and kidneys accumulate Cromolyn Sodium to any extent, prior to excretion of the compound unchanged in the bile and urine.

Similar studies in human volunteers have shown that only a small proportion of the administered dose is absorbed from the lung. A peak plasma level at 10 minutes was followed by a fall in concentration similar to that demonstrated in animal experiments.

Following inhalation of the powder aerosol, 3-5% of the dose was excreted in the urine over a 6 hour period. Assuming a similar rate of biliary excretion then approximately 10% of the administered dose was absorbed from the lung.

Other Routes of Administration

Following intravenous doses of Cromolyn Sodium, there is a rapid clearance of the compound from the plasma and a general distribution throughout the tissues with only the liver and kidneys accumulating the compound to any extent. Rapid excretion of the compound, unchanged, follows.

Intramuscular administration resulted in a pattern of absorption and excretion similar to that which occurs after intravenous administration. In the rat and dog no tissue accumulation could be detected after repeated intramuscular injections.

In the monkey, 6 hours after intravenous administration 80-90% of the total dose could be accounted for by biliary and renal excretion. At this stage, there is general distribution of the Cromolyn Sodium throughout the tissues with a higher concentration in the kidneys and liver. After intranasal administration of Cromolyn Sodium to rats, peak plasma levels occurred approximately 20 minutes after dosing.

The AUC_{0-3} corresponded to an absorption of 60% of the dose over 3 hours and the total amount of Cromolyn Sodium excreted in the bile over the same time period corresponded to an absorption of 53% of the dose administered.

In man, oral administration of Cromolyn Sodium is followed by a low rate of urinary excretion. In one study, the mean urinary excretion over 24 hours was only 0.5% of the dose administered.

This indicates that absorption of Cromolyn Sodium through the gastrointestinal tract is low.

TOXICOLOGY

Acute Toxicity

In acute toxicity tests in small laboratory animals the LD₅₀ on parenteral administration was usually between 2000 and 4000 mg/kg.

Subacute and Chronic Toxicity

In prolonged test in rats no toxic effects resulted from 90 daily subcutaneous injections except at doses greater than 30 mg/kg.

The only pathological lesion produced in any of these tests was an inflammation and degeneration of the renal tubules.

In Rhesus monkeys no evidence of renal or other toxicity could be found after 180 daily doses of 50 mg/kg had been given by the intravenous route. No toxicity was found in 90 day inhalation studies in rats, guinea pigs and monkeys.

In the case of the monkeys the drug was administered as a powder and each monkey received a capsule every 5 minutes for 6 hours a day, 5 days a week for 3 months. In none of these tests could any lung changes be detected nor were there any other indications of toxicity.

In one inhalation study using a group of 30 rats exposed to a concentration of 4.6 mg/L of air for one hour and three hours daily for 5 weeks, no toxic effects resulting from this treatment was observed.

A chronic inhalation toxicological study of Cromolyn Sodium was performed in the Squirrel monkey. Each of 5 experimental groups consisted of 3 male and 3 female monkeys.

Groups I and II were exposed 6 hr/day, 7 days/week, for 1 year to aerosols containing Cromolyn Sodium in approximate concentrations of 0.5 and 0.05 mg/liter of air, respectively. Group III animals were similarly exposed to an aerosol containing 0.01 of lactose/liter of air.

Group IV subjects served as chamber controls and the room controls (Group V) were maintained in the animal holding room throughout the study. A comprehensive toxicological evaluation of the monkeys was carried out prior to and throughout the study. No histopathological changes were seen in any variable.

Proliferative Arteriopathy in Macaque Monkeys

In four out of seven toxicity studies with Cromolyn Sodium, a proliferative arterial lesion has been found in some treated and untreated control macaque monkeys.

Although in these four studies, the proliferative arterial lesion occurred predominantly in the kidneys, such lesions were also found in other organs. In only one of these macaque monkey studies was there an increased incidence of the lesion in the drug treated group.

Further studies were therefore carried out in laboratories where Cromolyn Sodium had not been used.

PROLIFERATIVE ARTERITIS IN MACAQUE MONKEY IN CROMOLYN SODIUM STUDIES

Route	Duration	Overall	Control	Treated
Inhalation	3 months	0 in 18	0 in 6	0 in 12
Inhalation	4 months	7 in 30	2 in 18	5 in 12
Inhalation	4 months	2 in 45	1 in 18	1 in 27
Inhalation	3 months	2 in 25	1 in 17	1 in 8
I.V.	acute (7 days)	0 in 16	none	0 in 16
I.V.	acute (7 days)	1 in 8	0 in 2	1 in 6
I.V.	6 months	0 in 30	0 in 67	0 in 24
Total		9 in 172	2 in 67	7 in 105

Since the lesion has not been seen in chronic primate studies with baboons or squirrel monkeys treated for six months or longer with Cromolyn Sodium or in toxicity studies in rodents, it is inferred that the lesion may reflect a spontaneous disease of Macaque monkeys. The possibility that the increased incidence of the lesion in treated monkeys is due to the administration of Cromolyn Sodium can neither be affirmed nor refuted.

Teratogenicity

No teratogenic effects were seen in rabbits in which the compound was given intravenously, daily throughout pregnancy, in doses up to 250 mg/kg.

The latter dose was sufficient to cause severe damage to the maternal kidneys. At even higher doses (500 mg/kg) some partially resorbed foetuses showed developmental defects but all full-term foetuses were normal.

In rats dosed at 185 mg/kg daily s.c. throughout pregnancy, one foetus (out of 272) showed a grossly shortened humerus. No abnormalities were seen at lower doses (90 mg/kg). No teratogenic effect was seen in mice at daily doses of up to 540 mg/kg.

Safety in Pregnancy

A ten year study was recently completed in Sri Lanka (1982) to test the safety of Cromolyn Sodium in pregnancy. 296 pregnant asthmatic women, 18 to 44 years of age were maintained on a 20 mg capsule of Cromolyn Sodium, 2 to 3 times a day during a part or throughout the pregnancy. 292 of the pregnancies ended in the birth of a normal child whilst 4 infants (1.35%) had malformations. One example each was seen of a club foot, non-fused septum, harelip without cleft palate and patent ductus arteriosus.

Information on the incidence of congenital malformations within the Sri Lanka population is not available.

Epidemiological studies suggest that the incidence of abnormalities is 2-3% for the entire human population.

Cytotoxicity

At the cellular level, no effects of Cromolyn Sodium were observed at concentrations up to and including 1 mg/mL upon the following:

- Migration characteristics of guinea-pig macrophages
- Morphology of chick embryo-fibroblasts.
- Morphology of human epithelial cells from a cell line.
- Ciliary activity of samples of human ciliated epithelium.

Tests on human respiratory epithelium were undertaken to detect possible interference with pulmonary clearance mechanisms.

Effect on immune system

The effect of the drug on microbiological neutralizing systems including viruses *in vivo* and *in vitro* was studied. No effect was observed on: various antibody neutralizing or agglutinating systems: development of active immunity or antibody production; protection conferred by passive or active immunity. No effect was found on the following virus/antibody neutralizing systems *in vitro*: Influenza A, Polio Type II; with human or rabbit antiserum. Vaccinia; with rabbit antiserum. Herpes simplex; with human antiserum. None of the neutralization titres studied were affected by the presence of the compound up to concentrations of 1000 µg/mL. No effect was observed on the LD₅₀ in mice or in mouse adapted polio virus, nor on their protection by Salk-vaccine.

No effect was observed on the neutralization of clostridium welchii type A α toxin by specific antiserum, nor on several bacterial agglutinating systems tested. No effect was observed on the cytotoxic behaviour of rabbit anti-Hela cells *in-vitro*.

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