PRODUCT MONOGRAPH

APO-CROMOLYN NASAL SPRAY

Cromolyn Sodium Nasal Solution USP

2% w/v

Seasonal Allergic Rhinitis Prophylaxis

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PRODUCT MONOGRAPH

APO-CROMOLYN Nasal Spray

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2% w/v

THERAPEUTIC CLASSIFICATION

Seasonal Allergic Rhinitis Prophylaxis

ACTIONS AND CLINICAL PHARMACOLOGY

In the immediate allergic reaction (Type I) the union of antigen with reaginic antibody leads to the formation and release of spasmogens and other mediators of the anaphylactic reaction. Cromolyn sodium appears to block a step in the chain of events triggered by this union.

Cromolyn sodium has no antihistaminic, anti-inflammatory or decongestant activity. It reduces the symptoms of seasonal rhinitis by blocking the release of histamine and other mediators of immunity rather than blocking H_1-histamine receptors.

INDICATIONS AND CLINICAL USE

APO-CROMOLYN Nasal Spray (cromolyn sodium) is indicated for the prevention and relief of the nasal symptoms of seasonal allergic rhinitis, such as congestion (stuffy nose), sneezing and itchy, runny nose.

CONTRAINDICATIONS

A shown hypersensitivity to any of the ingredients of APO-CROMOLYN Nasal Spray (cromolyn

sodium), listed under the Composition section.

WARNINGS

If you do not obtain relief of your symptoms within 7 days of starting treatment, consult your doctor.

Patients with nasal polyps should not use this product except on the advice of a doctor.

If you are pregnant or nursing a baby, consult your doctor prior to use.

PRECAUTIONS

The experience in patients with nasal polyps is limited and therefore these patients should be carefully observed while undergoing treatment.

Possible immunologic changes resulting in reactions such as polymyositis, pneumonitis and heart failure, urticaria and anaphylaxis, have been reported.

Clinical experience in children under 5 years of age is limited.

During clinical use there have been, to date, no reports of adverse effects on the mother or the fetus which could be ascribed to the use of cromolyn sodium. Nevertheless, as with all medications, caution must be exercised during pregnancy.

ADVERSE REACTIONS

Occasionally, slight irritation of the nasal mucosa may occur. Cases of erythema, urticaria or maculopapular rash have been reported and these have cleared within a few days on withdrawal of the drug. Occasional headache, sneezing, cough and unpleasant taste in the mouth have been reported. Eosinophilic pneumonia has been reported rarely.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been no reported cases in humans of overdosage of the drug. Symptomatic treatment is suggested should overdosage occur.

DOSAGE AND ADMINISTRATION

APO-CROMOLYN (cromolyn sodium) therapy is a preventative measure, not a treatment.

It is recommended that treatment be instituted 1 week prior to the time at which the seasonal symptoms normally occur, and continued through the season, since cromolyn sodium is more effective if started prior to exposure to the offending allergen.

Dosage for both adults and children over 5 years of age

One metered-dose spray into each nostril 6 times daily (single dose 2.6 mg, total daily dose 15.6 mg cromolyn sodium). Do not exceed recommended dose.

Maintenance Therapy

When adequate response has been obtained, the frequency of inhalations may be reduced to one spray to each nostril 2-3 times per day (every 8 to 12 hours per day).

To help maintain relief, it is important to continue treatment throughout the allergy season even when you feel you are free of symptoms.

Concomitant Therapy

Due to the slow onset of action of this medication, other allergy medications may be used as required during **the first week** of therapy.

Withdrawal of APO-CROMOLYN therapy

Patients should be warned against suddenly discontinuing therapy when symptoms have been partially or completely controlled by APO-CROMOLYN.

As the action of APO-CROMOLYN is essentially preventative, continuity of therapy is important in patients who have gained benefit.

If for any reason APO-CROMOLYN is withdrawn, a suggested regimen for withdrawal is to reduce the APO-CROMOLYN dosage gradually over a period of one week. It should be borne in mind that symptoms of rhinitis may recur when APO-CROMOLYN is discontinued.

PHARMACEUTICAL INFORMATION

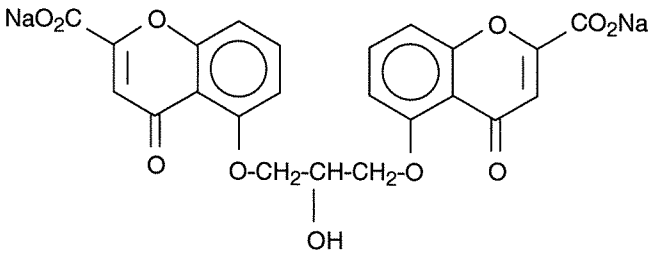
Drug Substance

Common Name: cromolyn sodium

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

(2) Disodium 5,5' –[(2–hydroxy–trimethylene) dioxy] bis[4–oxo–4*H*–1–benzopyran–2–carboxylate].

Structural Formula:



Molecular Formula: $C_{23}H_{14}Na_2O_{11}$

Molecular Weight: 512.34

Description: White or creamy white hygroscopic powder having little odour. It is tasteless at first but leaves a slightly bitter after-taste. It is soluble in water (1 in 20), and the resulting solution is neutral.

Composition

APO-CROMOLYN (cromolyn sodium) contains the following non-medicinal ingredients:

benzalkonium chloride, edetate disodium, purified water and sodium hydroxide.

Stability and Storage Recommendations

Store at room temperature (15 – 30°C). Preserve in tight, light-resistant containers.

AVAILABILITY OF DOSAGE FORMS

APO-CROMOLYN Nasal Spray (cromolyn sodium) is a clear, colourless to slightly yellowish solution, supplied in a high density polyethylene bottle with a pump attached to the bottle. The bottle contains not less than 26 mL (or not less than 13 mL) of solution. The pump delivers approximately 2.6 mg of cromolyn sodium (0.13 mL of the 2% w/v solution) per mist.

INFORMATION FOR THE CONSUMER

APO-CROMOLYN Nasal Spray

Cromolyn Sodium Nasal Solution USP, 2% w/v

Seasonal Allergic Rhinitis Prophylaxis

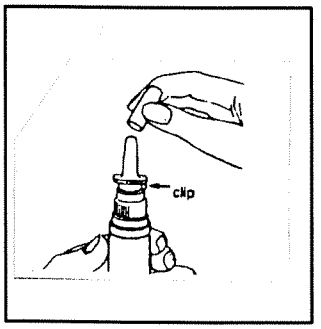
Instructions For Use

The solution is intended to prevent your symptoms from occurring. It is important to continue your treatment even when you are free from symptoms.

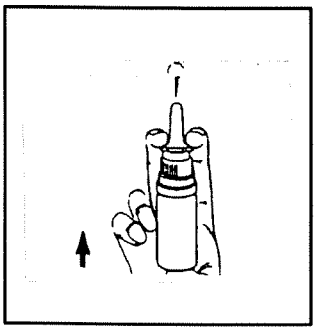
APO-CROMOLYN (cromolyn sodium) nasal metered-dose mist unit has a security clip around the neck of the pump. Remove the clip from the neck of the pump before use and replace after each use to prevent accidental activation of the pump.

Instructions

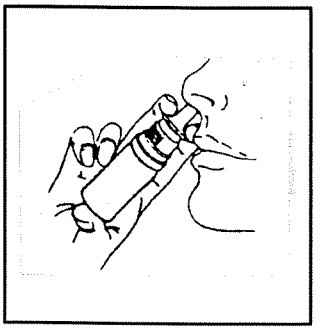
1) Remove dust cap from pump. Remove the security clip from around the neck of the pump.



2) Priming the Pump: Press the bottle upwards, as indicated by the arrow, then release. Repeat until one full mist is delivered.



3) Method of Use: Holding the bottle upright, insert the tip into the nostril and press the bottle fully upwards with thumb then release. This represents one dose. Repeat procedure for other nostril.



To keep clean, wipe nose piece and replace the dust cap after use. REPLACE THE SECURITY CLIP TO PREVENT ACCIDENTAL ACTIVATION.

Presentation

APO-CROMOLYN Nasal Spray is a 2% aqueous solution of cromolyn sodium containing benzalkonium chloride as an antimicrobial preservative, presented as a nasal metered-dose mist.

Indications

APO-CROMOLYN is indicated for the prevention and relief of the nasal symptoms of seasonal allergic rhinitis, such as congestion (stuffy nose), sneezing and itchy, runny nose.

Directions For Use

Since APO-CROMOLYN therapy is essentially preventive, it is important to maintain regular dosage, as distinct from using the drug intermittently to relieve symptoms.

Dosage and Administration

APO-CROMOLYN therapy is a preventative measure, not a treatment.

It is recommended that treatment be instituted 1 week prior to the time at which the seasonal symptoms normally occur, since cromolyn sodium is more effective if started prior to exposure to the offending allergen. Treatment should be continued throughout the allergy season.

DOSAGE for both adults and children over 5 years of age: 1 metered-dose spray into each nostril 6 times daily (single dose 2.6 mg, total daily dose 15.6 mg cromolyn sodium).

Do not exceed recommended dose.

MAINTENANCE THERAPY: When adequate response has been obtained, the dosage should be reduced to 2-3 times per day (every 8 to 12 hours per day).

One dose delivers approximately 0.13 mL of the 2% w/v solution.

To help maintain relief, it is important to continue treatment throughout the allergy season even when you feel you are free of symptoms. Treatment should not be discontinued abruptly but dosage should be reduced gradually over a period of one week.

Due to the slow onset of action of this medication, other allergy medications may be used as required during the first week of therapy.

Warnings

If you do not obtain relief of your symptoms within 7 days of starting treatment, consult your doctor.

Patients with nasal polyps should not use this product except on the advice of a doctor.

If you are pregnant or nursing a baby, consult your doctor prior to use.

Store at room temperature (15 – 30°C). Preserve in tight, light-resistant containers.

PHARMACOLOGY

In Vivo Studies in Animals

The principal effect of the drug is its specific ability to prevent disruption of sensitised cells and thus to inhibit the release of the mediators of anaphylaxis initiated by the interaction of antigen with reagin type antibodies.

The compound inhibited the passive cutaneous anaphylactic (PCA) reactions in monkeys (*Macaca speciosa*) sensitised with human reaginic serum when the compound was given intradermally with the antigen. It did not affect the skin reactions to intradermal histamine, 5–hydroxytryptamine or bradykinin. Antigen-induced histamine bronchoconstriction in anaesthetized marmosets (*Hapale jacchus*) sensitised intravenously with human reaginic serum was substantially reduced by cromolyn sodium compared with untreated controls.

Homologous PCA reactions with reagin-like antibody in rats using egg albumin/*B. pertussis* and *Nippostrongylus brasiliensis* sensitised systems showed complete inhibition in the presence of the compound. At the cellular level, it could be shown that cromolyn sodium, intravenously, markedly inhibited the rupture of sensitised rat mast cells from subcutaneous connective tissue. Although the drug inhibited PCA reaction, it failed to affect the skin lesions induced by compound 48/80, a potent histamine releaser.

In contrast, homologous PCA reactions with precipitating antibody in guinea-pigs were unaffected, as were aerosol or intravenous antigen-induced bronchospasm, and the release of histamine and slow-reacting substance (SRS-A) from actively or passively sensitised guinea-pig lung *in vitro*.

Other Experiments

The release of histamine and SRS-A from portions of fresh human lung passively sensitised with human reaginic serum was measured after exposure to specific antigens *in vitro*. Inhibition with cromolyn sodium was found over a narrow range of concentrations.

A further series of experiments, using the isolated ileum of the guinea-pig, confirmed that cromolyn sodium has no antagonizing action against the following spasmogens: histamine, serotonin (5-HT), acetylcholine, nicotine, substance P, bradykinin, or SRS-A.

Cromolyn sodium had no direct action in human bronchial chain *in vitro* nor did it antagonize the response to histamine, SRS-A, acetylcholine, or prostaglandin $F_{2\alpha}$.

These observations indicate that cromolyn sodium interferes with the release of spasmogens in some way following the union of antigen and reaginic antibody, but does not directly antagonize these spasmogens.

These studies emphasize that cromolyn sodium is most effective when given prior to antigen challenge.

Cromolyn sodium is neither a bronchodilator nor an anti-inflammatory agent and has a few general pharmacological effects. Its action is distinct from that of corticosteroids in that it appears to inhibit specifically the anaphylactic process initiated by reaginic antibody/antigen reactions.

Large doses of cromolyn sodium had only weak inconsistent effects on the cardiovascular and

respiratory systems of monkey, pig, cat, guinea-pig and rat.

In conscious and anaesthetized dogs, the drug activated chemoreceptors originating in the pulmonary and coronary circulations, mediated by the vagi, producing bradycardia, hypotension and sometimes apnoea.

In the anaesthetized marmoset, cromolyn sodium caused a rise in blood pressure and heart rate due to stimulation of post-ganglionic sympathetic fibres. The compound showed no significant effect in several anti-inflammatory tests.

Other experiments showed that the drug does not affect steroid metabolism as indicated by plasma corticosterone and adrenal ascorbic acid levels.

In experiments on isolated frog esophagus and human bronchial epithelium *in vitro* and on cat trachea *in vivo*, cromolyn sodium was used in high concentrations. There was no evidence that the compound interfered with pulmonary clearance. Further work on this aspect of the drug is in progress.

Absorption, Distribution and Excretion

The metabolism and tissue distribution of cromolyn sodium has been studied in mouse, rat, guinea-pig, rabbit, cat, dog, monkey (*Macaca speciosa*) and man. Cromolyn sodium, labelled with a radioactive isotope, tritium (^{3}H) has been used for the animal experiments and chemical and spectrofluorimetric methods of estimation for the experiments in man.

A) Inhalation Studies

Tritiated cromolyn sodium has been introduced as a fine powder aerosol into the lungs of rats, rabbits, and monkeys. All animals showed rapid clearance of the drug from the lungs, 50% being absorbed in 20 minutes, and 98% after 24 hours. The drug is taken up by the liver and kidneys and excreted unchanged via the bile and urine.

Human volunteers who inhaled the drug as a powder aerosol showed a peak plasma level at 15 minutes. This peak was followed by a fall in concentration similar to that demonstrated in the animal experiments. After inhalation, 3 – 5% of the administered dose was excreted in the urine over 6 hours. Assuming a similar biliary excretion, this would indicate that approximately 10% of the administered dose was absorbed.

B) Other Routes of Administration

Intravenous and intramuscular administration produces a rapid clearance of the compound from the plasma and a general distribution throughout the tissues followed by rapid excretion unchanged via the kidneys and in the bile. Intramuscular administration resulted in rapid absorption and excretion of a similar pattern to that following intravenous injection.

No tissue accumulation could be detected in the rat and dog after repeated intramuscular injections, the compound being excreted in the urine and bile. In the monkey, 6 hours after intravenous administration, 80 – 90% of the total dose could be accounted for by renal and biliary excretion. At this stage there is a general distribution of the compound

throughout the tissues with higher concentrations in the liver and kidney.

In man, oral administration of cromolyn sodium was followed by a low rate of urinary excretion. The mean urinary excretion of the administered dose over 24 hours was only 0.5%. This indicates that little of the compound is absorbed from the gastrointestinal tract.

TOXICOLOGY

Acute Toxicity

Cromolyn sodium was administered to a wide variety of animals by the intraperitoneal or the intravenous route. These animals included mice, rats (including newborn and sucking rats), guinea-pigs, rabbits, hamsters and monkeys. In most cases the LD_{50} was in the region of 4000 mg/kg and in all tests it was above 2000 mg/kg.

Subacute and Chronic Toxicity

Subcutaneous Injection – 90 day tests in rats: In one test, groups of 12 rats of each sex were injected daily for 90 days with subcutaneous doses of 30, 78 and 198 mg cromolyn sodium (tetrahydrate) per kg. At the two higher dose levels, some rats showed hemorrhage at the injection site and some showed renal tubular damage. The only other indications of toxic effects were in the higher dose male rats where the growth rates were depressed and the mean relative weights of the hearts and adrenals were significantly increased. These effects were probably secondary to the renal damage, which was most severe in this group. No effects were detected in the group dosed at 30 mg/ kg.

Intravenous Injection – 180 day test in monkeys: In this test, groups of 4 male and 4 female Rhesus monkeys were given daily intravenous injections of cromolyn sodium for 180 days at the following dose levels: 2, 10 and 50 mg/kg. No compound-induced effects were observed.

Proliferative Arteriopathy in Macaque Monkeys: A previously unreported proliferative arterial lesion has been found in some treated and untreated control Macaque monkeys in four out of seven toxicity studies with cromolyn sodium. In these four studies, the proliferative arterial lesion occurred predominantly in the kidneys, but was also found in other organs. An increased incidence of the lesion in the drug treated group occurred in one of these Macaque monkey studies. Subsequently the condition has been seen in other 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	5 in 30	1 in 18	4 in 12
Inhalation	4 months	2 in 45	1 in 18	1 in 27
Inhalation	3 months	1 in 25	0 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 6	0 in 24
TOTAL		9 in 172	2 in 67	7 in 105

The lesion has not been seen in chronic primates studies utilizing 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

In tests in rats, no fetal abnormalities were detected following daily subcutaneous injection of cromolyn sodium at 90 mg/kg throughout pregnancy with or without the addition of 0.05 mg of isoproterenol sulphate, these levels of each drug being sufficient to produce evidence of maternal toxicity. Even at a substantially higher dose level (185 mg/kg of cromolyn sodium alone) only one significant deformity (a shortened humerus) was seen in over 270 fetuses examined. Dosing at this level throughout the suckling period had no adverse effects on the young. Treatment of the males at 200 mg/kg for 85 days prior to mating did not affect their fertility.

In mice, daily subcutaneous doses of up to 540 mg/kg cromolyn sodium given during pregnancy caused no fetal malformations.

In rabbits, no teratogenic effect was detected when 250 mg/kg cromolyn sodium alone was given daily for the first 24 days of pregnancy by the intravenous route. At twice this dose, limb flexures were seen in 2 partially resorbed fetuses, but all 124 full-term fetuses produced were normal. Both these dose levels were sufficient to produce substantial tubular degeneration in the maternal kidneys.

Administration of subtoxic doses of cromolyn sodium either subcutaneously or intravenously to laboratory animals did not affect their reproductive performance and no teratogenic effects were

observed.

Safety in Pregnancy

A ten-year study was completed in Sri Lanka (1982) to test the safety of cromolyn sodium in pregnancy. Two hundred and ninety-six (296) pregnant asthmatic women, 18 to 44 years of age were maintained on a 20 mg capsule of cromolyn sodium, taken 2 to 3 times a day during a part or throughout the pregnancy. Two hundred and ninety-two (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

The effects of cromolyn sodium were studied at the cellular level. Various types of cells were incubated in different concentrations of the drug for several days. No effects were observed at concentrations up to and including 1000 μg/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.

The tests on human respiratory epithelium were included to detect potential interference with pulmonary clearance mechanisms.

Effects of Immune Systems

The precise way in which cromolyn sodium interferes with the release of spasmogens is not yet clear. The effect of the drug was studied on those antibody systems concerned with immunity. In this context, 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 antisera.

- Vaccinia; with rabbit antisera.

- Herpes simplex; with human antisera.

No effects were observed on the LD_{50} in mice or mouse-adapted polio virus, nor in their protection by Salk vaccine.

No effect was found on the neutralization of *Clostridium welchii* type A α-toxin by specific antiserum, nor on the cytotoxic behaviour of rabbit anti-HeLa serum on HeLa cells *in vitro*.

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