

PRODUCT MONOGRAPH

CROMOLYN EYE DROPS

Cromolyn Sodium Ophthalmic Solution, USP
2% w/v

Anti-allergic Agent

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THERAPEUTIC CLASSIFICATION

Anti-allergic Agent

ACTION AND CLINICAL PHARMACOLOGY

In the immediate allergic reaction (Type I) the union of antigen with reaginic antibody leads to the formation and release of the mediators of the local anaphylactic reaction. Cromolyn sodium (sodium cromoglycate) appears to block a step in the chain of events triggered by this union. The action appears to be specific for reaginic (immediate type) antigen/antibody reactions. No direct effect has been demonstrated on other types of immune reactions (Type II, III and IV).

Cromolyn sodium has no intrinsic bronchodilator, antihistaminic or anti-inflammatory activity.

In most patients, the signs and symptoms of seasonal allergic conjunctivitis (tearing, itching, congestion, etc.) can be expected to improve within 2-3 days of commencing treatment. With continued treatment, the patient will usually be free from ophthalmic signs and symptoms during the challenge period.

INDICATIONS AND CLINICAL USE

CROMOLYN EYE DROPS (cromolyn sodium) is indicated in the prevention of the signs and symptoms of seasonal allergic conjunctivitis (itching, tearing, congestion, etc.).

CONTRAINDICATIONS

CROMOLYN EYE DROPS (cromolyn sodium) is contraindicated in those patients who have shown hypersensitivity to any of its components.

WARNINGS

CROMOLYN EYE DROPS (cromolyn sodium) should not be used in the treatment of eye injury or infection. A doctor should be consulted immediately if the patient experiences any of the following:

- ▶ eye pain
- ▶ changes in vision
- ▶ pain on exposure to light

- ▶ redness of the eye
- ▶ excessive discharge
- ▶ abnormal pupils
- ▶ condition worsens or relief is not obtained within 72 hours

Not to be used with any other eye treatment except on the advice of a physician.

CROMOLYN EYE DROPS should be protected from direct sunlight. The opened bottle should be discarded after 4 weeks.

PRECAUTIONS

Soft contact lenses should not to be worn during treatment with CROMOLYN EYE DROPS (cromolyn sodium).

Safety and efficacy in children under 5 years of age have not been established.

Pregnancy and Lactation: During clinical use there have been, to date, no reports of adverse effects on the mother or the fetus which could be attributed to the use of cromolyn sodium. Caution must nevertheless be exercised during pregnancy and lactation.

ADVERSE REACTIONS

Transient ocular stinging or burning upon instillation has been observed as a frequently reported adverse reaction in patients using cromolyn sodium.

Watery, itchy eyes, conjunctival injection, dryness around the eyes, puffy eyes, eye irritation and sties have been reported as infrequent effects. It is not clear whether or not these reactions are due to the drug.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been no reported cases of overdosage with cromolyn sodium. Should overdosage occur, institute symptomatic treatment.

DOSAGE AND ADMINISTRATION

Adults and children 5 years of age and older: 1-2 drops in **each** eye 4 times a day **at regular intervals**.

Maximum single dose per eye: 2 drops (1.6 mg).

Maximum total daily dose per eye: 8 drops (6.4 mg).

CROMOLYN EYE DROPS (cromolyn sodium) should be used continually throughout the patient's usual allergy season, even when the patient is free of symptoms. Continued use could help ensure the patient remains symptom-free.

The effectiveness of CROMOLYN EYE DROPS therapy depends on its administration at regular intervals. It is therefore important to provide patients with clear instructions on the number of drops to be taken daily and the regular use of the product. In addition, the patient should be instructed to replace the cap after use and to avoid touching the eye or other surfaces with the applicator tip (to maintain sterility).

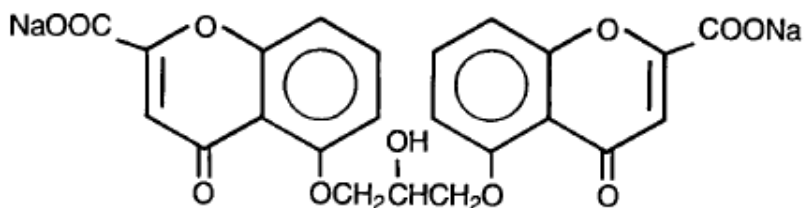
PHARMACEUTICAL INFORMATION

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

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

CROMOLYN EYE DROPS (cromolyn sodium) is a 2% (w/v) solution of cromolyn sodium, USP in purified water and disodium EDTA. Benzalkonium chloride 0.01% is added as a preservative.

Stability and Storage Recommendations

Store at 15°C-30°C. Protect from light.

AVAILABILITY OF DOSAGE FORMS

CROMOLYN EYE DROPS (cromolyn sodium) is supplied in plastic dropper bottles containing 5 mL, 10 mL, or 12.5 mL of a sterile 2% (w/v) solution of cromolyn sodium.

INFORMATION FOR THE CONSUMER

CROMOLYN EYE DROPS

(CROMOLYN SODIUM OPHTHALMIC SOLUTION USP 2% w/v)

CROMOLYN EYE DROPS is a non-prescription drug intended to be used for the **prevention and relief** of the eye symptoms of *seasonal allergic conjunctivitis*. Please read the following information carefully as it will guide you in the safe use of this medication.

What is seasonal allergic conjunctivitis?

If your eyes are itching, watery and swollen, and your nasal passages are congested and runny, you may be suffering from seasonal allergic conjunctivitis. This type of allergy is most often caused on a seasonal basis by exposure to airborne substances such as pollen, grasses, weeds, dust and/or animal dander.

What is the difference between an eye infection and an allergic reaction in the eye?

An eye infection is caused by a pathogenic agent (microorganism or virus) which can multiply and produce inflammation, pain, excessive or milky discharge, altered vision and pain on exposure to light. If you experience any of these symptoms, you must consult your doctor immediately. Your doctor can accurately identify the infectious agent and prescribe appropriate treatment.

In contrast, an allergic reaction in the eye is caused by the individual's own sensitivity to a substance (allergen) that would not normally cause a reaction. The symptoms produced by the reaction (itchy, watery and swollen eyes etc.) are seldom characteristic of serious eye disease. Usually these symptoms are only annoying and may be treated with a non-prescription product such as CROMOLYN EYE DROPS. However, if you are not sure about the seriousness of your condition, or if you are experiencing your eye symptoms for the first time, you should contact your doctor. See the list below for the types of serious eye conditions requiring the attention of a doctor.

Eye conditions requiring the attention of a doctor

- Pain
- Changes in vision (double vision, spotty vision etc.)
- Pain on exposure to light (photophobia)
- Acute redness of the eye
- Excessive or milky (non-clear) discharge
- Abnormal pupils
- Injury (chemical, mechanical etc.)
- Conditions lasting longer than 72 hours

What is CROMOLYN EYE DROPS, and how does it work?

During an allergic reaction, various substances are released by certain cells in your eyes. These are called mast cells. The substances released by these cells affect your eyes in different ways. For example, they affect blood vessels, nerves, and glands – causing redness, itching and watery eyes. CROMOLYN EYE DROPS acts on the mast cells to **prevent** them from releasing the substances that cause these problems.

How you should take CROMOLYN EYE DROPS to make it work best for you?

- This drug is only intended for use in adults and children 5 years of age and older.
- Use the dropper to apply 1 to 2 drops in each eye 4 times a day at regular intervals; the effect of CROMOLYN EYE DROPS therapy depends on its administration at regular intervals.
Maximum single dose per eye: 2 drops (1.6 mg).
Maximum total daily dose per eye: 8 drops (6.4 mg)..
- Do not exceed the recommended dose.
- **To avoid contamination** of this product, do not touch dropper tip to eyes or to any other surface. Replace cap after use.
- Wash your hands before and after using CROMOLYN EYE DROPS.
- Seek the advice of a healthcare professional if you are not sure how to apply the drops in your eyes, or how to administer them in a child's eyes.
- CROMOLYN EYE DROPS should be used continually throughout your usual allergy season, even when you feel you are free of symptoms. Continued use could help ensure that you remain symptom-free.

Warnings:

- CROMOLYN EYE DROPS should only be used for allergic conditions of the eye. Do not use it in the treatment of eye injury or infection.
- Irritation or redness may be due to a serious eye condition such as infection, foreign body in the eye, or other mechanical or chemical corneal injury requiring the attention of a doctor.
- If you experience eye pain, changes in vision, pain on exposure to light, acute redness of the eye, excessive or milky (non-clear) discharge, abnormal pupils, or if condition worsens or persists for more than 72 hours, consult your doctor immediately.
- Do not wear soft contact lenses during treatment with CROMOLYN EYE DROPS.
- Do not use CROMOLYN EYE DROPS with any other eye treatment except on the advice of your doctor.
- If you are pregnant or nursing a baby, consult your doctor before using CROMOLYN EYE DROPS.
- Protect this medication from direct sunlight.
- Do not use if the solution changes colour or becomes cloudy.
- Discard the bottle 4 weeks after opening.

What you should remember before taking this medication:

Remember that CROMOLYN EYE DROPS is used for the prevention of the symptoms caused by seasonal allergies. It should **not be** used in the treatment of a serious eye condition. Read the above information or speak to your pharmacist to help determine if you have an eye problem that requires the attention of a doctor. Keep this leaflet for future reference.

To store this medicine:

- Keep out of reach of children.
- Store between 15°C and 30°C. The container should be tightly closed and protected from light.
- Discard the bottle 4 weeks after opening. Be sure that any discarded medicine is out of the reach of children.

Contains benzalkonium chloride as a preservative.

PHARMACOLOGY

Animal Pharmacology: 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 (type II) antibodies.

When cromolyn sodium was administered intradermally with human reagin serum to macaque monkeys 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-hydroxytryptamine. Using anaesthetized marmosets, 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 albumen/*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 apnea. These effects were caused by stimulation of the post-ganglionic sympathetic fibres. 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 parasympathetic system, producing bradycardia, hypotension, bradypnea and sometimes apnea.

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.

Studies have been performed on the distribution, metabolism, and excretion of cromolyn sodium in the mouse, rat, guinea-pig, rabbit, cat, dog, monkey and man. The drug was administered by the intravenous, oral and nasal (rat) routes, as well as by inhalation. Tritium-labelled cromolyn sodium has been used for the animal studies, whereas ¹⁴C-labelled drug, radioimmunoassay, HPLC, and spectrophotometric 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 by 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 to 5% of the dose was excreted in the urine over a 6-hour period. Assuming a similar rate of biliary excretion, 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 unchanged compound 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 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 a 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 effect 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 1 and 2 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/L of air, respectively. Group 3 animals were similarly exposed to an aerosol containing 0.01 mg lactose/L of air. Group 4 subjects served as chamber controls and the room controls (Group 5) 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.

Studies of Cromolyn Sodium Ophthalmic Solution: A 28 day irritancy test of rabbit eyes was conducted using 4% cromolyn sodium ophthalmic solution applied to one eye up to four times daily. Assessment of the reaction (Draize method) showed cromolyn sodium solution was non irritant to the cornea, iris or conjunctiva, and no drug-related gross or microscopic changes were observed.

Studies of 2% cromolyn sodium ophthalmic solution were carried out in the New Zealand albino rabbit (3 months) and squirrel monkey (6 months). Each experimental group consisted of 4 males

and 4 females. Two drops of cromolyn sodium solution were instilled into both eyes of each high dose animal, two to ten times daily. The control animals were treated similarly with placebo solution only. No fundoscopic changes were seen. Detailed histopathological examination of eyes and related structures revealed no local irritation or toxic effects of treatment.

Drug Interaction Studies: No incompatibility could be detected in the rabbit eye when cromolyn sodium 4% ophthalmic solution was used with the following commonly used ophthalmic drugs:

A. Drugs given once daily for 5 days:

- Topiramide 0.5% (Mydracyl 0.5% ophthalmic solution)
- Phenylephrine hydrochloride 10% (Neo-Synephrine 10% ophthalmic solution)
- Cyclopentolate hydrochloride 0.5% (Cyclogyl 0.5% ophthalmic solution)

B. Drugs given once daily for 28 days:

VASOCONSTRICTORS

- Tetrahydrozoline HCl 0.05% (Visine ophthalmic solution)
- Murine ophthalmic Solution

ANTIBODIES

- Gentamycin sulfate (Garamycin ophthalmic solution)
- Chloramphenicol 0.5% (Choromycetin 0.5% ophthalmic solution)
- Polymyxin B - neomycin - gramicidin (Neosporin ophthalmic solution)
- Sodium sulfacetamide 30% (sodium Sulamyd 30% ophthalmic solution)

ASTRINGENTS

- Zinc sulfate 0.25% (Zincfrin ophthalmic solution)

STEROIDS

- Dexamethasone sodium phosphate 0.1% (Decadron 0.1% ophthalmic solution)
- Prednisolone acetate 1% + phenylephrine 0.12% (Prednefrin Forte 1% aqueous suspension).

Teratology: 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 fetuses showed developmental defects but all full-term fetuses were normal. In rats dosed at 185 mg/kg daily s.c. throughout pregnancy, one fetus (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.

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.

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, Polio (with human or rabbit anti serum); Vaccinia (with rabbit antiserum); Herpes simplex (with human antiserum).

None of the neutralization titres studied was 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*.

Carcinogenesis and Mutagenesis: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation) and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium. No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

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