# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**75-271**

# APPROVED DRAFT LABELING

Maego

# Cromolyn Sodium Inhalation Solution USP

**20 mg/2 mL**

**RX Only**

**FOR ORAL INHALATION USE ONLY**

**Each Low Density Polyethylene Vial Contains:**
20 mg cromolyn sodium USP, in water for injection USP.

Attention Pharmacist Ensure the package insert entitled "Patient's Instructions for Use" is dispensed with solution. See package insert for Dosage and Administration.
Store between 15° and 30°C (59° and 86°F). Protect from light.
Do not use if solution is discolored or contains a precipitate.
Retain in foil pouch until time of use.

**5 x 2 mL Sterile Unit Dose Vials**

**Manufactured for:**
**Zenith Goldline Pharmaceuticals Inc., MIAMI, FL 33137**
**By: Steripak Ltd., Runcorn, Cheshire WA7 1QF England**

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# CROMOLYN SODIUM INHALATION SOLUTION, USP

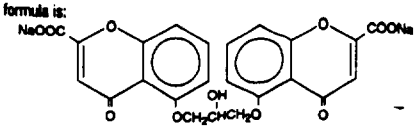
## PRESCRIBING INFORMATION

**Rx only**

**For Oral Inhalation Use Only - Not for Injection**

**DESCRIPTION:** The active ingredient of cromolyn sodium inhalation solution USP is cromolyn sodium, USP. It is an inhaled anti-inflammatory agent for the preventive management of asthma. Cromolyn sodium is chemically designated as disodium 5,5'- [(2-hydroxytrimethylene)dioxy] bis [4-oxo-4*H*-1-benzopyran-2-carboxylate]. The molecular formula is $C_{23}H_{14}Na_2O_{11}$; the molecular weight is 512.34. Cromolyn sodium is a water-soluble, odorless, white, hydrated crystalline powder. It is tasteless at first, but leaves a slightly bitter aftertaste. Cromolyn sodium is clear, colorless to pale yellow, sterile and has a target pH of 5.5.

The structural formula is:




Each 2 mL vial for oral inhalation use only contains 20 mg cromolyn sodium, USP in water for injection, USP.

**CLINICAL PHARMACOLOGY:** *In vitro* and *in vivo* animal studies have shown that cromolyn sodium inhibits sensitized mast cell degranulation which occurs 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 inhibits both the immediate and non-immediate bronchoconstrictive reactions to inhaled antigen. Cromolyn sodium also attenuates bronchospasm caused by exercise, toluene diisocyanate, aspirin, cold air, sulfur dioxide and environmental pollutants.

Cromolyn sodium has no intrinsic bronchodilator or antihistaminic activity.

After administration by inhalation, approximately 8% of the total cromolyn sodium dose administered is absorbed and rapidly excreted unchanged, approximately equally divided between urine and bile. The remainder of the dose is either exhaled or deposited in the oropharynx, swallowed and excreted via the alimentary tract.

**INDICATIONS AND USAGE:** Cromolyn sodium inhalation solution, USP is a prophylactic agent indicated in the management of patients with bronchial asthma.

In patients whose symptoms are sufficiently frequent to require a continuous program of medication, cromolyn sodium inhalation solution, USP is given by inhalation on a regular daily basis (see **DOSAGE AND ADMINISTRATION**). The effect of cromolyn sodium is usually evident after several weeks of treatment, although some patients show an almost immediate response.

In patients who develop acute bronchoconstriction in response to exposure to exercise, toluene diisocyanate, environmental pollutants, etc, cromolyn sodium should be given shortly before exposure to the precipitating factor (see **DOSAGE AND ADMINISTRATION**).

**CONTRAINDICATIONS:** Cromolyn sodium inhalation solution, USP is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium.

**WARNINGS: Cromolyn sodium inhalation solution, USP has no role in the treatment of status asthmaticus.**

Anaphylactic reactions with cromolyn sodium administration have been reported rarely.

**PRECAUTIONS: General:** Occasionally, patients may experience cough and/or bronchospasm following inhalation of cromolyn sodium. At times, patients who develop bronchospasm may not be able to continue cromolyn sodium administration despite prior bronchodilator administration. Rarely, very severe bronchospasm has been encountered.

Symptoms of asthma may recur if cromolyn sodium is reduced below the recommended dosage or discontinued.

**Information for Patients:** Cromolyn sodium is to be taken as directed by the physician. Because it is preventive medication, it may take up to four weeks before the patient experiences maximum benefit.

Cromolyn sodium should be used in a power-driven nebulizer with an adequate airflow rate equipped with a suitable face mask or mouthpiece.

Drug stability and safety of cromolyn sodium inhalation solution when mixed with other drugs in a nebulizer have not been established.

For additional information, see the accompanying leaflet entitled Living a Full Life with Asthma.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies of cromolyn sodium in mice (12 months intraperitoneal administration at doses up to 150 mg/kg three days per week), hamsters (intraperitoneal administration at doses up to 53 mg/kg three days per week for 15 weeks followed by 17.5 mg/kg three days per week for 37 weeks), and rats (18 months subcutaneous treatment at doses up to 75 mg/kg six days per week) showed no neoplastic effects. These doses correspond to approximately 1, 0.3, and 2 times, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis.

Cromolyn sodium showed no mutagenic potential in Ames Salmonella/microsome plate assays, mitotic gene conversion in *Saccheromyces cerevisiae* and an *in vitro* cytogenetic study in human peripheral lymphocytes.

No evidence of impaired fertility was shown in laboratory reproduction studies conducted subcutaneously in rats at the highest doses tested, 175 mg/kg/day in males and 100 mg/kg/day in females. These doses are approximately 18 and 10 times, respectively, the maximum recommended adult human daily inhalation dose on a mg/m² basis.

**Pregnancy: Teratogenic Effects, Pregnancy Category B.** Reproduction studies with cromolyn sodium administered subcutaneously to pregnant mice and rats at maximum daily doses of 540 mg/kg and 164 mg/kg, respectively, and intravenously to rabbits at a maximum daily dose of 485 mg/kg produced no evidence of fetal malformations. These doses represent approximately 27, 17, and 98 times, respectively, the maximum recommended adult human daily inhalation dose on a mg/m² basis. Adverse fetal effects (increased resorption and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Drug Interaction During Pregnancy:** Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses up to 540 mg/kg (approximately 27 times the maximum recommended adult daily inhalation dose on a mg/m² basis) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (approximately 7 times the maximum recommended adult human daily inhalation dose on a mg/m² basis) increased both resorptions and malformations. The addition of cromolyn sodium to isoproterenol appears to have increased the incidence of both resorptions and malformations.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when cromolyn sodium is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

**ADVERSE REACTIONS:** Clinical experience with the use of cromolyn sodium suggests that adverse reactions are rare events. The following adverse reactions have been associated with cromolyn sodium : cough, nasal congestion, nausea, sneezing and wheezing.

Other reactions have been reported in clinical trials; however, a causal relationship could not be established: drowsiness, nasal itching, nose bleed, nose burning, serum sickness, and stomachache.

In addition, adverse reactions have been reported with cromolyn sodium for inhalation, USP capsules. The most common side effects are associated with inhalation of the powder and include transient cough (1 in 5 patients) and mild wheezing (1 in 25 patients). These effects rarely require treatment or discontinuation of the drug.

Information on the incidence of adverse reactions to cromolyn sodium for inhalation, USP capsules has been derived from U.S. postmarketing surveillance experience. The following adverse reactions attributed to cromolyn sodium, based upon recurrence following readministration, have been reported in less than 1 in 10,000 patients: laryngeal edema, swollen parotid gland, angioedema, bronchospasm, joint swelling and pain, dizziness, dysuria and urinary frequency, nausea, cough, wheezing, headache, nasal congestion, rash, urticaria and lacrimation.

Other adverse reactions have been reported in less than 1 in 100,000 patients, and it is unclear whether these are attributable to the drug: anaphylaxis, nephrosis, periarteritic vasculitis, pericarditis, peripheral neuritis, pulmonary infiltrates with eosinophilia, polymyositis, exfoliative dermatitis, hemoptysis, anemia, myalgia, hoarseness, photodermatitis and vertigo.

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**OVERDOSAGE:** There is no clinical syndrome associated with an overdosage of cromolyn sodium. Acute toxicity testing in a wide variety of species has demonstrated an extremely low order of toxicity for cromolyn sodium, regardless of whether administration was parenteral, oral or by inhalation. Parenteral administration in mice, rats, guinea pigs, hamsters and rabbits demonstrated an $LD_{50}$ in the region of 4000 mg/kg. Intravenous administration in monkeys also indicated a similar pattern of toxicity. The highest dose administered by the oral route in rats and mice was 8000 mg/kg, and at this dose level no deaths occurred. By inhalation, even in long term studies, it proved impossible to achieve toxic dose levels of cromolyn sodium in a range of mammalian species.

**DOSAGE AND ADMINISTRATION:** For management of bronchial asthma in adults and pediatric patients (two years of age and over), the usual starting dosage is the contents of one vial administered by nebulization four times a day at regular intervals.

Drug stability and safety of cromolyn sodium inhalation solution when mixed with other drugs in a nebulizer have not been established.

Patients with chronic asthma should be advised that the effect of cromolyn sodium inhalation solution, USP therapy is dependent upon its administration at regular intervals, as directed. Cromolyn sodium inhalation solution, USP should be introduced into the patient's therapeutic regimen when the acute episode has been controlled, the airway has been cleared and the patient is able to inhale adequately.

For the prevention of acute bronchospasm which follows exercise or exposure to cold dry air, environmental agents (e.g., animal danders, toluene diisocyanate, pollutants), etc., the usual dose is the contents of one vial administered by nebulization shortly before exposure to the precipitating factor.

**It should be emphasized to the patient that the drug is poorly absorbed when swallowed and is not effective by this route of administration.**

**Cromolyn Sodium Inhalation Solution, USP Therapy in Relation to Other Treatments for Asthma: Non-steroidal agents:** Cromolyn sodium inhalation solution, USP should be *added* to the patient's existing treatment regimen (e.g., bronchodilators). When a clinical response to cromolyn sodium inhalation solution, USP is evident, usually within two to four weeks, and if the asthma is under good control, an attempt may be made to decrease concomitant medication usage gradually.

If concomitant medications are eliminated or required on no more than a prn basis, the frequency of administration of cromolyn sodium inhalation solution, USP may be titrated downward to the lowest level consistent with the desired effect. The usual decrease is from four to three vials per day. It is important that the dosage be reduced gradually to avoid exacerbation of asthma. It is emphasized that in patients whose dosage has been titrated to fewer than four vials per day, an increase in the dose of cromolyn sodium inhalation solution, USP and the introduction of, or increase in, symptomatic medications may be needed if the patient's clinical condition deteriorates.

**Corticosteroids:** In patients chronically receiving corticosteroids for the management of bronchial asthma, the dosage should be maintained following the introduction of cromolyn sodium inhalation solution, USP. If the patient improves, an attempt to decrease corticosteroids should be made. Even if the corticosteroid-dependent patient fails to show symptomatic improvement following cromolyn sodium inhalation solution, USP administration, the potential to reduce corticosteroids may nonetheless be present. Thus, gradual tapering of corticosteroid dosage may be attempted. It is important that the dose be reduced slowly, maintaining close supervision of the patient to avoid an exacerbation of asthma.

It should be borne in mind that prolonged corticosteroid therapy frequently causes an impairment in the activity of the hypothalamic-pituitary-adrenal axis and a reduction in the size of the adrenal cortex. A potentially critical degree of impairment or insufficiency may persist asymptomatically for some time even after gradual discontinuation of adrenocortical steroids. Therefore, if a patient is subjected to significant stress, such as a severe asthmatic attack, surgery, trauma or severe illness while being treated or within one year (occasionally up to two years) after corticosteroid treatment has been terminated, consideration should be given to reinstituting corticosteroid therapy. When respiratory function is impaired, as may occur in severe exacerbation of asthma, a temporary increase in the amount of corticosteroids may be required to regain control of the patient's asthma.

It is particularly important that great care be exercised if, for any reason, cromolyn sodium inhalation solution, USP is withdrawn in cases where its use has permitted a reduction in the maintenance dose of corticosteroids. In such cases, continued close supervision of the patient is essential since there may be sudden reappearance of severe manifestations of asthma which will require immediate therapy and possible reintroduction of corticosteroids.

For additional information, see the accompanying leaflet entitled Living a Full Life with Asthma.

**HOW SUPPLIED:** Cromolyn Sodium Inhalation Solution Unit Dose 2 mL Vial is supplied as a colorless to pale yellow solution containing 20mg cromolyn sodium, USP, in water for injection, USP, with 5 vials per foil pouch in cartons as listed below.

60 vials per carton. (NDC 0172-6406-49).

120 vials per carton. (NDC 0172-6406-59).

Each vial is made from a low density polyethylene (LDPE) resin.

**Store between 15° and 30°C (59° and 86°F) and protect from light. Do not use if solution is discolored or contains a precipitate.**

Retain in foil pouch until time of use.

**KEEP OUT OF THE REACH OF CHILDREN.**

Manufactured for: ZENITH GOLDLINE PHARMACEUTICALS, INC., MIAMI, FL 33137
by: Stanpak Limited, Runcorn, Cheshire WA7 1QF England
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