DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

APR - 4 2000

David Garbe
Director, Scientific Information and Medical Compliance
Allergan, Inc.
2525 DuPont Drive TL-1L
PO Box 19534
Irvine, CA 92623-9534

RE: **NDA 21-009**
Alocril (nedocromil sodium ophthalmic solution), 2%
MACMIS # 8809

Dear Mr. Garbe:

This letter describes Allergan, Inc.'s (Allergan) violative promotional materials for Alocril submitted February 29, 2000, under cover of Form FDA 2253. The submission included a Dear Doctor letter, two sales aids (AL9172 and AL9245), a fold-out brochure titled, "The Chain of Ocular Itch in Allergic Response Is About To Be Broken," and a journal advertisement. The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed these promotional materials and concluded that they are false or misleading under the Federal Food, Drug, and Cosmetic Act and its implementing regulations because they contain unsubstantiated claims and de-emphasize risk information. Our specific objections follow:

Misleading Classification

In the Dear Doctor letter, you claim that Alocril is a **new class** of mast cell stabilizer (emphasis added). This claim is misleading because it is not supported by adequate evidence. Alocril's approved product labeling states that nedocromol sodium [Alocril] is a mast cell stabilizer. Alocril's description from the clinical pharmacology section of the approved product labeling is similar to other marketed products with mast cell stabilizing properties that alleviate itching due to allergic conjunctivitis. Thus, to imply that Alocril is a new class of mast cell stabilizer without adequate evidence is misleading.

Unsubstantiated Comparison

In many of the promotional materials[1], you claim that in a comparative study of symptomatic relief in cat-sensitive individuals (n=20), Alocril provides symptomatic

1. Brochures AL9245 and AL9172, Dear Doctor letter, and unnumbered advertisement

relief as fast as Patanol. This claim is misleading because it is not supported by substantial evidence. You have referenced an active controlled study in 20 patients using olepatadine hydrochloride 0.1% and 2% nedocromil sodium to assess burning and itching. This study is inadequately designed and powered to support your claim that Alocril and Patanol have similar speeds of effectiveness.

Fair Balance

The promotional materials lack fair balance because they fail to present information relating to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug. For example:

Brochure AL9245 - Although information is presented regarding the side effects seen with Alocril, this information is presented less prominently than your claims of efficacy. For example, the most detailed information is placed inconspicuously in paragraph format on the bottom of the last page of the brochure below the company information and product logo. However, the efficacy information is presented in easy-to-read short bulleted statements.

Advertisement - The risk information is presented in block, running text and is placed on the bottom of the page of the advertisement below the company information and product logo.

Dear Doctor Letter - The risk information is presented in block, running text and is placed on the bottom of the page below the Director of Marketing's signature block.

Requested Action

Because of these unsubstantiated claims and lack of fair balance, we request that you immediately cease the dissemination of these violative promotional materials and any other violative promotional materials that lack fair balance and/or make false or misleading claims regarding Alocril. You should respond to me regarding this violation by April 18, 2000, providing a list of the promotional materials discontinued and the date Allergan ceased the dissemination of the promotional materials.

If you have any questions, please contact me by facsimile at (301) 594-6771, or write to me at the Division of Drug Marketing. Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 8809 and NDA 21-009.

Sincerely,

/S/

Warren F. Rumble
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

Alocril
nedocromil sodium ophthalmic solution 2%

Dear Doctor:

Until now, your choices in treating itch due to allergic conjunctivitis have generally been limited to treatments that provided relief in either the early (immediate) or late (delayed) phase of the ocular allergic response—but not both. New ALOCRIL™ (nedocromil sodium ophthalmic solution) 2% gives you **year-round power to break the chain of ocular itch in the allergic response whenever allergies strike**—quickly, safely, and with proven efficacy.

Powerful year-round relief whenever allergies strike.

ALOCRIL™, a fast-acting (within minutes), new class of mast cell stabilizer, is indicated for the treatment of itch due to allergic conjunctivitis. It has been shown to relieve both the early- and late-phase symptoms of allergic conjunctivitis[1,2] by inhibiting histamines,[2,3] decreasing chemotaxis,[3,4] and inhibiting secondary inflammatory cells.

Powerful speed with long-lasting results.

ALOCRIL™ works just as fast as the antihistamines you may currently be prescribing. In fact, ALOCRIL™ ophthalmic solution matched the speed of Patanol® in a comparative study of ocular itch in cat-sensitive individuals (N = 20).[5] (No significant difference at 15 minutes.) And in an environmental study of symptom control (N = 79), **77% of ALOCRIL™ patients reported experiencing relief within 15 minutes and 37% within 2 minutes.**[6] But that's not all. ALOCRIL™ provides effective relief of ocular itch with just twice-daily dosing. And unlike many other ocular allergy products, ALOCRIL™ ophthalmic solution provides protection throughout the period of exposure, even in the absence of symptoms.

Power with safety.

ALOCRIL™ has been proven safe to use in children 3 years of age and older and has a Pregnancy Category B rating. However, this product should be used in pregnant or nursing women only as clearly needed. There are no contraindications to the use of ALOCRIL™ ophthalmic solution with other ocular products.

Feel the power.

Your Allergan representative will be calling on you in early March to explain how new ALOCRIL™ puts the power to stop ocular itch due to allergic conjunctivitis right where it belongs—in your hands. Try ALOCRIL™ ophthalmic solution in your allergic conjunctivitis patients; then compare the results you achieve with those produced by antihistamines, traditional first-generation mast cell stabilizers, topical corticosteroids, and nonsteroidal anti-inflammatory drugs. Once you feel the power of ALOCRIL™, you may never let go.

Sincerely,

Kevin Skule
Director of Marketing

The most frequently reported adverse experience was headache (~ 40%). Ocular burning, irritation, and stinging; unpleasant taste; and nasal congestion have been reported to occur in 10% to 30% of patients. Other events occurring between 1% and 10% included asthma, conjunctivitis, eye redness, photophobia, and rhinitis. Some of these events were similar to those produced by the underlying ocular disease and/or vehicle being studied. Please see other side for full prescribing information.

1. Church MK, Hutson PA, Holgate ST. Effect of nedocromil sodium on early and late phase responses to allergen challenge in the guinea-pig. *Drugs*. 1989;37(suppl 1):101-108. 2. Conn R. Nedocromil sodium: a review of the evidence for a dual mechanism of action in the treatment of allergic conjunctivitis. *Clin Exp Allergy*. In press. 3. Eady RP. The pharmacology of nedocromil sodium. *Eur J Respir Dis*. 1986;69(suppl 147):112-119. 4. Bruijnzeel PLB, Warringa RAJ, Kok PTM, Kreukniet J. Inhibition of neutrophil and eosinophil induced chemotaxis by nedocromil sodium and sodium cromoglycate. *Br J Pharmacol*. 1990;99:798-802. 5. Raizman MB, Rothman JS. A comparative study of Patanol® and 2% nedocromil sodium eye drops [ALOCRIL™] in the treatment of allergic conjunctivitis in cat sensitive individuals. Presented at: Annual Meeting of the American College of Allergy, Asthma & Immunology; November 12-17, 1999; Chicago, Ill. 6. Alexander M, Rosen LJ, Yang WH. Comparison of topical nedocromil sodium and oral terfenadine for the treatment of seasonal allergic conjunctivitis. *Clin Ther*. 1999;21(11):1900-1907.

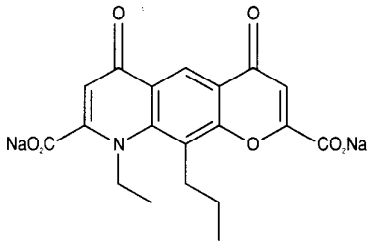
www.alocril.com

50 years GROWTH & INNOVATION

ALOCRIL™ (nedocromil sodium ophthalmic solution) 2%
Sterile

DESCRIPTION
ALOCRIL™ (nedocromil sodium ophthalmic solution) 2% is a clear, yellow, sterile solution for topical ophthalmic use.

Nedocromil sodium is represented by the following structural formula:



$C_{19}H_{15}NNa_2O_7$ Mol. Wt. 415.30 CAS: 69049-47-7

Chemical Name: 4H-Pyrano[3.2-g] quinoline-2, 8-dicarboxylic acid, 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-, disodium salt.

Each mL Contains: Active: Nedocromil sodium 20 mg (2%); **Preservative:** Benzalkonium chloride 0.01%; **Inactives:** Sodium chloride 0.5%, edetate disodium 0.05% and purified water. It has a pH of 4.0 to 5.5.

CLINICAL PHARMACOLOGY
Nedocromil sodium is a mast cell stabilizer. Nedocromil sodium inhibits the release of mediators from cells involved in hypersensitivity reactions. Decreased chemotaxis and decreased activation of eosinophils have also been demonstrated.

In vitro studies with adult human bronchoalveolar cells showed that nedocromil sodium inhibits histamine release from a population of mast cells having been defined as belonging to the mucosal sub type and beta-glucuronidase release from macrophages.

Pharmacokinetics and Bioavailability
Nedocromil sodium exhibits low systemic absorption. When administered as a 2% ophthalmic solution in adult human volunteers, less than 4% of the total dose was systemically absorbed following multiple dosing. Absorption is mainly through the nasolacrimal duct rather than through the conjunctiva. It is not metabolized and is eliminated primarily unchanged in urine (70%) and feces (30%).

INDICATIONS AND USAGE
ALOCRIL™ is indicated for the treatment of itching associated with allergic conjunctivitis.

CONTRAINDICATIONS
ALOCRIL™ is contraindicated in those patients who have shown hypersensitivity to nedocromil sodium or to any of the other ingredients.

PRECAUTIONS
Information for Patients
Patients should be advised to follow the patient instructions listed on the Information for Patients sheet.

Users of contact lenses should refrain from wearing lenses while exhibiting the signs and symptoms of allergic conjunctivitis.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
A two-year inhalation carcinogenicity study of nedocromil sodium at a dose of 24 mg/kg/day (approximately 400 times the maximum recommended human daily ocular dose on a mg/kg basis) in Wistar rats showed no carcinogenic potential.

Nedocromil sodium showed no mutagenic potential in the Ames Salmonella/microsome plate assay, mitotic gene conversion in *Saccharomyces cerevisiae*, mouse lymphoma forward mutation and mouse micronucleus assays.

Reproduction and fertility studies in mice and rats showed no effects on male and female fertility at a subcutaneous dose of 100 mg/kg/day (more than 1600 times the maximum recommended human daily ocular dose).

Pregnancy: Teratogenic Effects: Pregnancy Category B
Reproduction studies performed in mice, rats and rabbits using a subcutaneous dose of 100 mg/kg/day (more than 1600 times the maximum human daily ocular dose on a mg/kg basis) revealed no evidence of teratogenicity or harm to the fetus due to nedocromil sodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ALOCRIL™ should be used during pregnancy only if clearly needed.

Nursing Mothers
After intravenous administration to lactating rats, nedocromil was excreted in milk. 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 ALOCRIL™ is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children below the age of 3 years have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS
The most frequently reported adverse experience was headache (~40%).

Ocular burning, irritation and stinging, unpleasant taste, and nasal congestion have been reported to occur in 10 - 30% of patients. Other events occurring between 1 - 10% included asthma, conjunctivitis, eye redness, photophobia, and rhinitis.

Some of these events were similar to the underlying ocular disease being studied.

DOSAGE AND ADMINISTRATION
The recommended dosage is one or two drops in each eye twice a day. ALOCRIL™ should be used at regular intervals.

Treatment should be continued throughout the period of exposure (i.e., until the pollen season is over or until exposure to the offending allergen is terminated), even when symptoms are absent.

HOW SUPPLIED
ALOCRIL™ (nedocromil sodium ophthalmic solution) 2% is supplied as 5 mL of solution in a natural, low-density polyethylene round eye drop bottle with a controlled dropper tip, and a natural polypropylene cap.

5 mL NDC 0023-8842-05

Storage
Store between 2° - 25°C (36° - 77°F). Keep tightly closed and out of the reach of children.

Rx Only

Manufactured by
Rhone-Poulenc Rorer
Le Trait, France

Distributed by
Allergan
Irvine, CA 92612, USA

71338US10E
8729X

FOR THE TREATMENT OF OCULAR ITCH DUE TO ALLERGIC CONJUNCTIVITIS...

BREAK THE CHAIN OF OCULAR ITCH IN THE ALLERGIC RESPONSE.

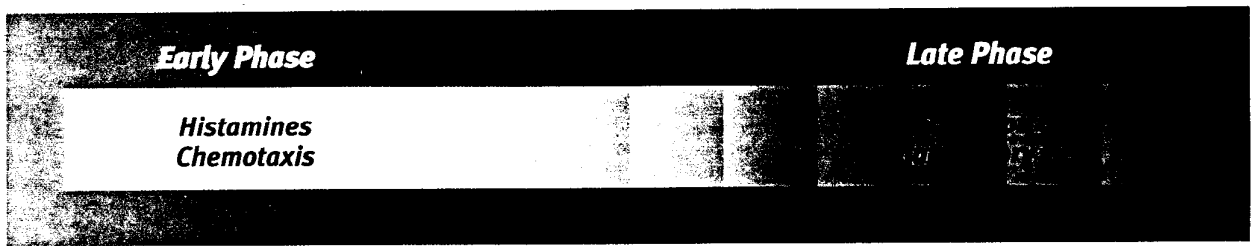
AL-9172.

NEW Alocril™
(nedocromil sodium ophthalmic solution) 2%
The power to stop ocular itch.

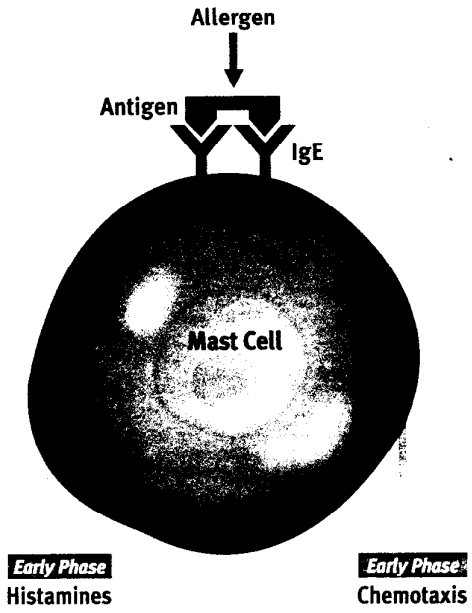
New ALOCRIL™

The power to stop ocular itch.

YEAR-ROUND RELIEF WHENEVER ALLERGIES STRIKE.



- ALOCRIL™ ophthalmic solution has the power to provide effective relief in both the early and late phases of the allergic response.[1,2]



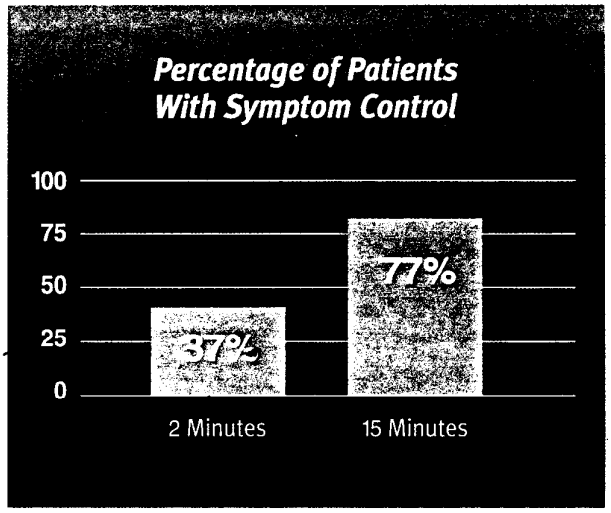
POWERFUL RESULTS.

- By inhibiting histamines,[2,3] decreasing chemotaxis,[3,4] and inhibiting secondary inflammatory cells, ALOCRIL™ produces a significant effect on the allergic response.
- Provides protection throughout the period of exposure, even in the absence of symptoms.
- Users of contact lenses should refrain from wearing lenses while exhibiting the signs and symptoms of allergic conjunctivitis.

Powerful duration with the speed of an antihistamine.

POWERFUL SPEED.

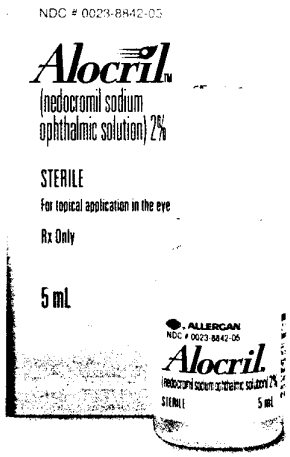
- As fast as Patanol® in a comparative study of ocular itch in cat-sensitive individuals (N = 20).[5] (No significant difference at 15 minutes.)
- Relief in minutes—in an environmental study (N = 79), 77% of ALOCRIL™ patients reported experiencing relief within 15 minutes and 37% within 2 minutes.[6]



Patient response to ALOCRIL™ in an environmental study.[6]

POWERFUL DURATION.

- Effective relief with just twice-daily dosing.



NEW Alocril™
(nedocromil sodium ophthalmic solution) 2%
The power to stop ocular itch.

The most frequently reported adverse experience was headache (~ 40%). Ocular burning, irritation, and stinging; unpleasant taste; and nasal congestion have been reported to occur in 10% to 30% of patients. Other events occurring between 1% and 10% included asthma, conjunctivitis, eye redness, photophobia, and rhinitis.

Some of these events were similar to those produced by the underlying ocular disease and/or vehicle being studied.

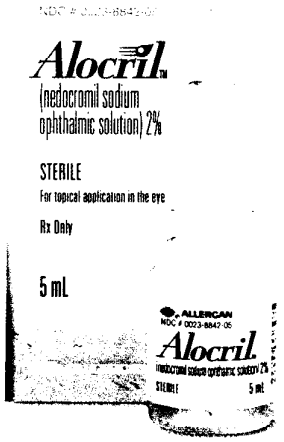
FOR THE TREATMENT OF OCULAR ITCH DUE TO ALLERGIC CONJUNCTIVITIS...

New ALOCRIL™

Breaks the chain of ocular itch in the allergic response.

- Effective relief in both the early and late phases of the allergic response.[1,2]
- Powerful, year-round relief whenever allergies strike.
- Works in minutes,[6] with just twice-daily dosing.
- Continued protection throughout the period of exposure, even in the absence of symptoms.
- Proven safe and effective for children 3 years of age and up.
- No contraindications with other ocular products.

NEW Alocril™
(nedocromil sodium ophthalmic solution) 2%
The power to stop ocular itch.



Note to representative: Please provide full prescribing information when presenting this material.

1. Church MK, Hutson PA, Holgate ST. Effect of nedocromil sodium on early and late phase responses to allergen challenge in the guinea-pig. *Drugs.* 1989;37(suppl 1):101-108.
2. Corin R. Nedocromil sodium: a review of the evidence for a dual mechanism of action in the treatment of allergic conjunctivitis. *Clin Exp Allergy.* In press.
3. Eady RP. The pharmacology of nedocromil sodium. *Eur J Respir Dis.* 1986;69(suppl 147):112-119.
4. Bruijnzeel PLB, Warringa RAJ, Kok PTM, Kreukniet J. Inhibition of neutrophil and eosinophil induced chemotaxis by nedocromil sodium and sodium cromoglycate. *Br J Pharmacol.* 1990;99:798-802.
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6. Alexander M, Rosen LJ, Yang WH. Comparison of topical nedocromil sodium and oral terfenadine for the treatment of seasonal allergic conjunctivitis. *Clin Ther.* 1999;21(11):1900-1907.

www.alocril.com

AL9172

FOR THE TREATMENT OF OCULAR ITCH
DUE TO ALLERGIC CONJUNCTIVITIS...

BREAK THE CHAIN OF OCULAR ITCH IN THE ALLERGIC RESPONSE.

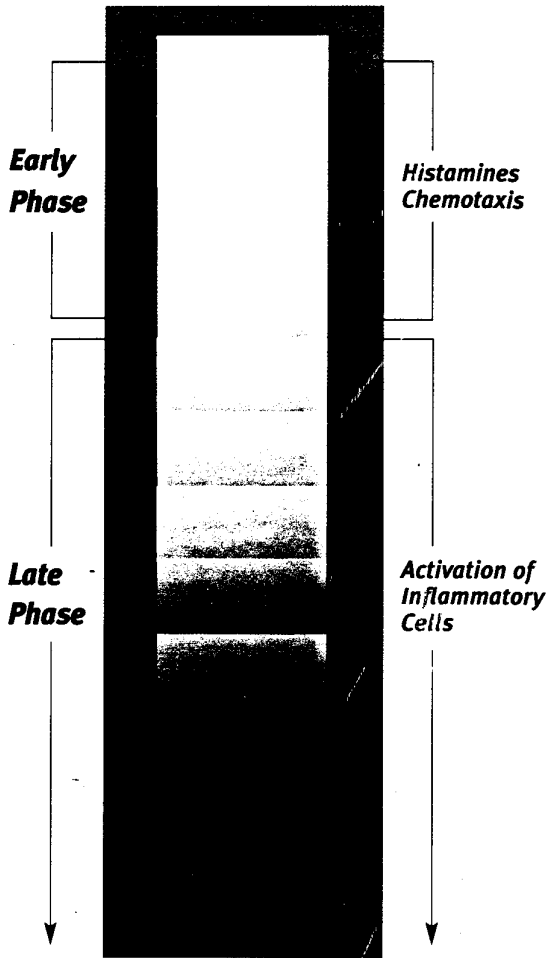
AL 9245

NEW Alocril.
(nedocromil sodium ophthalmic solution) 2%
The power to stop ocular itch.

New ALOCRIL™

The power to stop ocular itch.

Phases of the Ocular Allergic Response

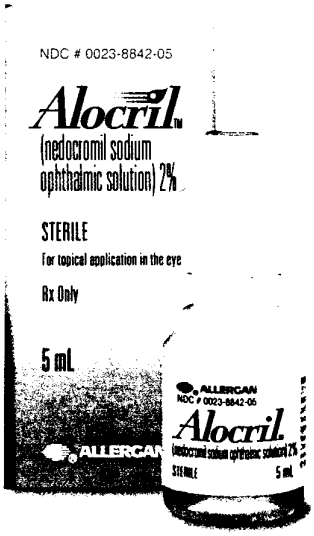


Safety and effectiveness in children below the age of 3 years have not been established.

Please see full prescribing information and references on last pages.

YEAR-ROUND RELIEF WHENEVER ALLERGIES STRIKE.

- ALOCRIL™ ophthalmic solution has the power to provide effective relief in both the early and late phases of the allergic response.[1,2]

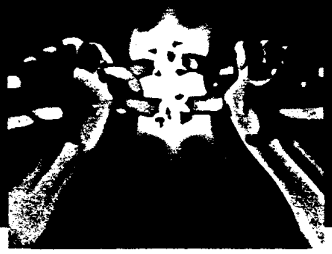


NEW Alocril
(nedocromil sodium ophthalmic solution) 2%

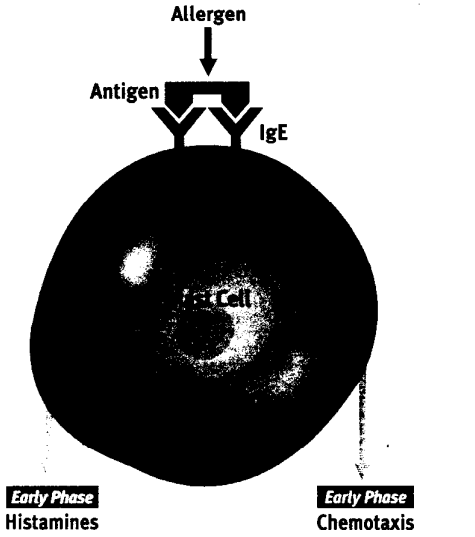
The power to stop ocular itch.

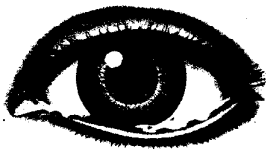
New ALOCRIL™

The power to stop ocular itch.



Mechanism of Action of the Ocular Allergic Response





POWERFUL RESULTS.

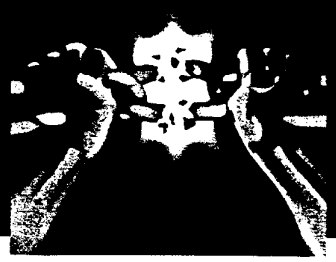
- By inhibiting histamines,[2,3] decreasing chemotaxis,[3,4] and inhibiting secondary inflammatory cells, ALOCRIL™ ophthalmic solution produces a significant effect on the allergic response.
- Provides protection throughout the period of exposure, even in the absence of symptoms.
- Users of contact lenses should refrain from wearing lenses while exhibiting the signs and symptoms of allergic conjunctivitis.

Please see full prescribing information and references on last pages.

NEW Alocril®
(nedocromil sodium ophthalmic solution) 2%
The power to stop ocular itch.

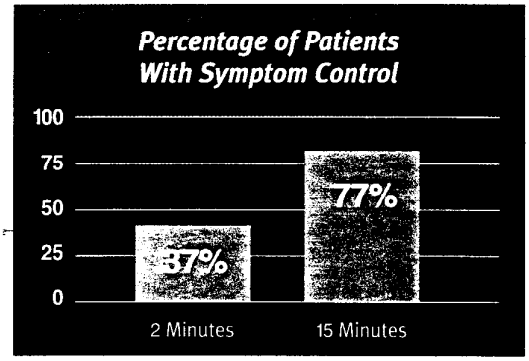
New ALOCRIL™

Powerful duration with the speed of an antihistamine.



POWERFUL SPEED.

- As fast as Patanol® in a comparative study of ocular itch in cat-sensitive individuals (N = 20). (No significant difference at 15 minutes.)[5]
- Relief in minutes—in an environmental study (N = 79), 77% of ALOCRIL™ ophthalmic solution patients reported experiencing relief within 15 minutes and 37% within 2 minutes.[6]



Patient response to ALOCRIL™ in an environmental study.[6]

POWERFUL DURATION.

- Effective relief with just twice-daily dosing.

POWER WITH SAFETY.

- Proven safe and effective in children 3 years of age and above.
- No contraindications with other ocular products.

The most frequently reported adverse experience was headache (~ 40%). This event was similar to that produced by the underlying ocular disease and/or vehicle being studied.

Please see full prescribing information and references on last pages.

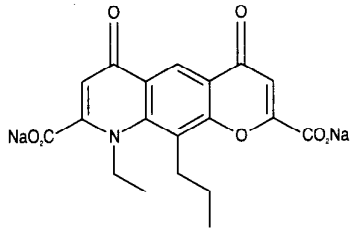
NEW Alocril
(nedocromil sodium ophthalmic solution) 2%

The power to stop ocular itch.

ALOCRIL™
(nedocromil sodium ophthalmic solution) 2% Sterile

DESCRIPTION
ALOCRIL™ (nedocromil sodium ophthalmic solution) 2% is a clear, yellow, sterile solution for topical ophthalmic use.

Nedocromil sodium is represented by the following structural formula:



$C_{19}H_{15}NNa_2O_7$ Mol. Wt. 415.30 CAS: 69049-47-7

Chemical Name: 4H-Pyrano[3,2-g] quinoline-2, 8-dicarboxylic acid, 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-propyl-, disodium salt.

Each mL contains: Active: Nedocromil sodium 20 mg (2%); **Preservative:** Benzalkonium chloride 0.01%; **Inactives:** Sodium chloride 0.5%, edetate disodium 0.05% and purified water. It has a pH of 4.0 to 5.5.

CLINICAL PHARMACOLOGY
Nedocromil sodium is a mast cell stabilizer. Nedocromil sodium inhibits the release of mediators from cells involved in hypersensitivity reactions. Decreased chemotaxis and decreased activation of eosinophils have also been demonstrated.

In vitro studies with adult human bronchoalveolar cells showed that nedocromil sodium inhibits histamine release from a population of mast cells having been defined as belonging to the mucosal sub type and beta-glucuronidase release from macrophages.

Pharmacokinetics and Bioavailability
Nedocromil sodium exhibits low systemic absorption. When administered as a 2% ophthalmic solution in adult human volunteers, less than 4% of the total dose was systemically absorbed following multiple dosing. Absorption is mainly through the nasolacrimal duct rather than through the conjunctiva. It is not metabolized and is eliminated primarily unchanged in urine (70%) and feces (30%).

INDICATIONS AND USAGE
ALOCRIL™ is indicated for the treatment of itching associated with allergic conjunctivitis.

CONTRAINDICATIONS
ALOCRIL™ is contraindicated in those patients who have shown hypersensitivity to nedocromil sodium or to any of the other ingredients.

PRECAUTIONS
Information for Patients
Patients should be advised to follow the patient instructions listed on the Information for Patients sheet.

Users of contact lenses should refrain from wearing lenses while exhibiting the signs and symptoms of allergic conjunctivitis.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
A two-year inhalation carcinogenicity study of nedocromil sodium at a dose of 24 mg/kg/day (approximately 400 times the maximum recommended human daily ocular dose on a mg/kg basis) in Wistar rats showed no carcinogenic potential.

Nedocromil sodium showed no mutagenic potential in the Ames Salmonella/microsome plate assay, mitotic gene conversion in *Saccharomyces cerevisiae*, mouse lymphoma forward mutation and mouse micronucleus assays. Reproduction and fertility studies in mice and rats showed no effects on male and female fertility at a subcutaneous dose of 100 mg/kg/day (more than 1600 times the maximum recommended human daily ocular dose).

Pregnancy: Teratogenic Effects: Pregnancy Category B
Reproduction studies performed in mice, rats and rabbits using a subcutaneous dose of 100 mg/kg/day (more than 1600 times the maximum human daily ocular dose on a mg/kg basis) revealed no evidence of teratogenicity or harm to the fetus due to nedocromil sodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ALOCRIL™ should be used during pregnancy only if clearly needed.

Nursing Mothers
After intravenous administration to lactating rats, nedocromil was excreted in milk. 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 ALOCRIL™ is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children below the age of 3 years have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS
The most frequently reported adverse experience was headache (~40%). Ocular burning, irritation and stinging, unpleasant taste, and nasal congestion have been reported to occur in 10 - 30% of patients. Other events occurring between 1 - 10% included asthma, conjunctivitis, eye redness, photophobia, and rhinitis.

Some of these events were similar to the underlying ocular disease being studied.

DOSAGE AND ADMINISTRATION

The recommended dosage is one or two drops in each eye twice a day. ALOCRIL™ should be used at regular intervals.

Treatment should be continued throughout the period of exposure (i.e., until the pollen season is over or until exposure to the offending allergen is terminated), even when symptoms are absent.

HOW SUPPLIED

ALOCRIL™ (nedocromil sodium ophthalmic solution) 2% is supplied as 5 mL of solution in a natural, low-density polyethylene round eye drop bottle with a controlled dropper tip, and a natural polypropylene cap.

5 mL NDC 0023-8842-05

Storage

Store between 2° - 25°C (36° - 77°F). Keep tightly closed and out of the reach of children.

Rx Only

Manufactured by
Rhone-Poulenc Rorer
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References:

1. Church MK, Hutson PA, Holgate ST. Effect of nedocromil sodium on early and late phase responses to allergen challenge in the guinea-pig. *Drugs.* 1989;37(suppl 1): 101-108.
2. Corin R. Nedocromil sodium: a review of the evidence for a dual mechanism of action in the treatment of allergic conjunctivitis. *Clin Exp Allergy.* In press.
3. Eady RP. The pharmacology of nedocromil sodium. *Eur J Respir Dis.* 1986;69 (suppl 147):112-119.
4. Bruijnzeel PLB, Warringa RAJ, Kok PTM, Kreukniet J. Inhibition of neutrophil and eosinophil induced chemotaxis by nedocromil sodium and sodium cromoglycate. *Br J Pharmacol.* 1990;99:798-802.
5. Raizman MB, Rothman JS. A comparative study of Patanol® and 2% nedocromil sodium eye drops [ALOCRIL™] in the treatment of allergic conjunctivitis in cat sensitive individuals. Presented at: Annual Meeting of the American College of Allergy, Asthma & Immunology; November 12-17, 1999; Chicago, Ill.
6. Alexander M, Rosen LJ, Yang WH. Comparison of topical nedocromil sodium and oral terfenadine for the treatment of seasonal allergic conjunctivitis. *Clin Ther.* 1999;21(11):1900-1907.

NEW Alocril
(nedocromil sodium ophthalmic solution) 2%
The power to stop ocular itch.

FOR THE TREATMENT OF OCULAR ITCH DUE TO ALLERGIC CONJUNCTIVITIS...

New ALOCRIL™

Breaks the chain of ocular itch in the allergic response.

- Effective relief in both the early and late phases of the allergic response.[1,2]
- Powerful year-round relief whenever allergies strike.
- Works in minutes,[6] with just twice-daily dosing.
- Continued protection throughout the period of exposure, even in the absence of symptoms.
- Proven safe and effective for children 3 years of age and up.
- No contraindications with other ocular products.

NEW Alocril
(nedocromil sodium ophthalmic solution) 2%

The power to stop ocular itch.

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Ocular burning, irritation, and stinging; unpleasant taste; and nasal congestion have been reported to occur in 10% to 30% of patients. Other events occurring between 1% and 10% included asthma, conjunctivitis, eye redness, photophobia, and rhinitis.

Some of these events were similar to those produced by the underlying ocular disease and/or vehicle being studied.

Please see full prescribing information and references on last pages.

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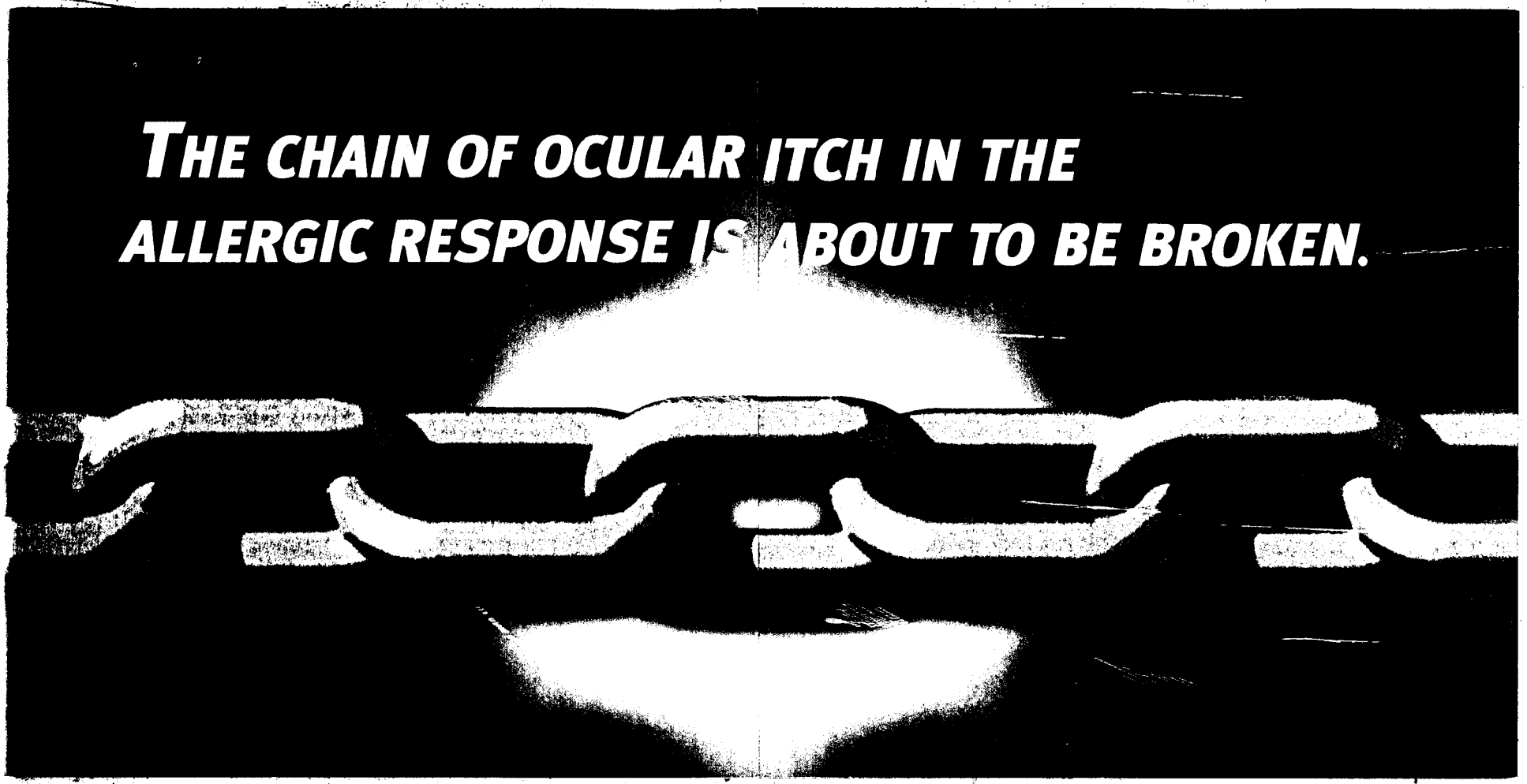
AL9245


THE CHAIN OF OCULAR ITCH IN THE
ALLERGIC RESPONSE IS ABOUT TO BE BROKEN.

1. Church MK, Hutson PA, Holgate ST. Effect of nedocromil socium on early and late phase responses to allergen challenge in the guinea-pig. *Drugs*. 1989;37(suppl 1):101-108. 2. Corin R. Nedocromil sodium: a review of the evidence for a dual mechanism of action in the treatment of allergic conjunctivitis. *Clin Exp Allergy*. In press. 3. Raizman MB, Rothman JS. A comparative study of Patanol™ and 2% nedocromil sodium eye drops (ALOCRIL™) in the treatment of allergic conjunctivitis in cat sensitive individuals. Presented at: Annual Meeting of the American College of Allergy, Asthma & Immunology; November 12-17, 1999; Chicago, Ill. 4. Alexander M, Rosen LJ, Yang WH. Comparison of topical nedocromil sodium and oral terfenadine for the treatment of seasonal allergic conjunctivitis. *Clin Ther*. 1999;21(11):1900-1907. 5. ALOCRIL™ Prescribing Information.

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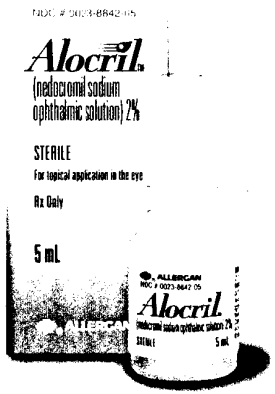
50 Years of Growth & Innovation

The power to stop ocular itch

YEAR-ROUND RELIEF WHENEVER ALLERGIES STRIKE.

Clinical studies indicate that new ALOCRIL™ ophthalmic solution gives you the power to stop itch due to allergic conjunctivitis—year-round, no matter when allergies strike. That means you can provide relief to patients who present in the late phase of the allergic response as well as those who present much earlier, when symptoms first occur.[1,2] In fact, ALOCRIL™ continues to provide protection throughout the period of exposure, even in the absence of symptoms.



The most frequently reported adverse experience was headache (~ 40%). Ocular burning, irritation, and stinging; unpleasant taste; and nasal congestion have been reported to occur in 10% to 30% of patients. Other events occurring between 1% and 10% included asthma, conjunctivitis, eye redness, photophobia, and rhinitis.

Some of these events were similar to those produced by the underlying ocular disease and/or vehicle being studied.

tch in the allergic response.

In a comparative study of ocular itch in cat-sensitive individuals (N = 20), ALOCRIL™ ophthalmic solution was shown to be just as fast as Patanol®. (No significant difference at 15 minutes.)[3] And in an environmental study (N = 79), 77% of ALOCRIL™ patients reported experiencing relief within 15 minutes and 37% within 2 minutes.[4]

POWERFUL DURATION WITH THE SPEED OF AN ANTIHISTAMINE.

Importantly, these results were obtained with just twice-daily dosing. What's more, ALOCRIL™ ophthalmic solution is safe to use in children 3 years of age and older and it has a Pregnancy Category B rating.[5] However, this product should be used in pregnant or nursing women only as clearly needed. ALOCRIL™ may be safely used with other ocular products.

Give your patients the chance to break the chain of ocular itch in the allergic response in a brand new way. Prescribe new ALOCRIL™ today.

NEW Alocril
(nedocromil sodium ophthalmic solution) 2%

The power to stop ocular itch.

www.alocril.com

Please see full prescribing information enclosed.

FOR THE TREATMENT OF ITCH
DUE TO ALLERGIC CONJUNCTIVITIS...

BREAK THE CHAIN OF OCULAR ITCH IN THE ALLERGIC RESPONSE.

POWERFUL YEAR-ROUND RELIEF WHENEVER ALLERGIES STRIKE.

- The power to decrease chemotaxis[1,2] combined with mast cell stabilization, for effective relief in both the early and late phases of the allergic response.[3,4]

POWERFUL RESULTS.

- Continued protection throughout the period of exposure, even in the absence of symptoms.

POWERFUL SPEED.

- The speed of an antihistamine, with relief in minutes.[5,6]

POWERFUL DURATION.

- Effective relief with just twice-daily dosing.

NEW Alocril®
(nedocromil sodium ophthalmic solution) 2%
The power to stop ocular itch.

The most frequently reported adverse experience was headache (~ 40%). Ocular burning, irritation, and stinging; unpleasant taste; and nasal congestion have been reported to occur in 10% to 30% of patients. Other events occurring between 1% and 10% included asthma, conjunctivitis, eye redness, photophobia, and rhinitis. Some of these events were similar to those produced by the underlying ocular disease and/or vehicle being studied.

Please see adjacent page for brief prescribing information.

1. Eady RP. The pharmacology of nedocromil sodium. *Eur J Respir Dis.* 1986;69(suppl 147):112-119. 2. Bruijnzeel PLB, Warringa RAJ, Kok PTM, Kreukniet J. Inhibition of neutrophil and eosinophil-induced chemotaxis by nedocromil sodium and sodium cromoglycate. *Br J Pharmacol.* 1990;99:798-802. 3. Church MK, Hutson PA, Holgate ST. Effect of nedocromil sodium on early and late phase responses to allergen challenge in the guinea pig. *Drugs.* 1989;37(suppl 1):101-108. 4. Corn R. Nedocromil sodium: a review of the evidence for a dual mechanism of action in the treatment of allergic conjunctivitis. *Clin Exp Allergy.* In press. 5. Alexander M, Ronli LI, Yang WH. Comparison of topical nedocromil sodium and oral terfenadine for the treatment of seasonal allergic conjunctivitis. *Clin Ther.* 1999;21(11):1900-1907. 6. Raizman MB, Rothman LS. A comparative study of Patanol® and Alocril® eye drops. ALOCRIL® in the treatment of allergic conjunctivitis in cat sensitive individuals. Presented at: Annual Meeting of the American College of Allergy, Asthma & Immunology; November 12-17, 1999; Chicago, Ill.

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ALOCRIL™ (nedocromil sodium ophthalmic solution) 2%
Sterile

INDICATIONS AND USAGE
ALOCRIL™ is indicated for the treatment of itching associated with allergic conjunctivitis.

CONTRAINDICATIONS
ALOCRIL™ is contraindicated in those patients who have shown hypersensitivity to nedocromil sodium or to any of the other ingredients.

PRECAUTIONS
Information for Patients
Patients should be advised to follow the patient instructions listed on the information for Patients sheet.

Users of contact lenses should refrain from wearing lenses while exhibiting the signs and symptoms of allergic conjunctivitis.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
A two-year inhalation carcinogenicity study of nedocromil sodium at a dose of 24 mg/kg/day (approximately 400 times the maximum recommended human daily ocular dose on a mg/kg basis) in Wistar rats showed no carcinogenic potential.

Nedocromil sodium showed no mutagenic potential in the Ames Salmonella/microsome plate assay, mitotic gene conversion in *Saccharomyces cerevisiae*, mouse lymphoma forward mutation and mouse micronucleus assays.

Reproduction and fertility studies in mice and rats showed no effects on male and female fertility at a subcutaneous dose of 100 mg/kg/day (more than 1600 times the maximum recommended human daily ocular dose).

Pregnancy: Teratogenic Effects: Pregnancy Category B
Reproduction studies performed in mice, rats and rabbits using a subcutaneous dose of 100 mg/kg/day (more than 1600 times the maximum human daily ocular dose on a mg/kg basis) revealed no evidence of teratogenicity or harm to the fetus due to nedocromil sodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ALOCRIL™ should be used during pregnancy only if clearly needed.

Nursing Mothers
After intravenous administration to lactating rats, nedocromil was excreted in milk. 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 ALOCRIL™ is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children below the age of 3 years have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS
The most frequently reported adverse experience was headache (~40%).

Ocular burning, irritation and stinging, unpleasant taste, and nasal congestion have been reported to occur in 10 - 30% of patients. Other events occurring between 1 - 10% included asthma, conjunctivitis, eye redness, photophobia, and rhinitis.

Some of these events were similar to the underlying ocular disease being studied.

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Le Trait, France

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