

PRODUCT MONOGRAPH

ALOCRITM

nedocromil sodium ophthalmic solution

2% w/v

ANTI-ALLERGIC

**Allergan Inc.
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PRODUCT MONOGRAPH

ALOCRITM

nedocromil sodium ophthalmic solution

2% w/v

THERAPEUTIC CLASSIFICATION

Anti-Allergic

CLINICAL PHARMACOLOGY

ALOCRITM is a 2% ophthalmic preparation of nedocromil sodium that displays specific anti-allergic and anti-inflammatory properties.

The pharmacological actions of nedocromil sodium in many respects resemble those of sodium cromoglycate, a compound which has been shown to have effects on both the symptoms of ocular allergic inflammation and the level of inflammatory mediators present in the tears.^{3,42} Nedocromil sodium is not only an inhibitor of the immunological release of inflammatory mediators, but also extends this activity to mucosal mast cells, which are thought to play an important role in allergic inflammatory diseases.⁵⁻¹⁵ The conclusion that nedocromil sodium is an anti-inflammatory agent is supported by *in vivo* observations of its capacity to inhibit the late response to antigen challenge,¹⁶⁻³⁰ microvascular leakage^{32,33} and platelet activating factor (PAF) induced bronchoconstriction and hyperresponsiveness^{34,35,36,38}. In the dog and guinea-pig, nedocromil sodium has been shown to modify sensory nerve responses, a possible mechanism for its observed inhibitory effects on reflex bronchoconstriction and cough^{39,40}.

When administered as 2% ophthalmic solution in human volunteers, up to 4% of a dose of nedocromil sodium is absorbed; absorption occurs primarily through the nasal mucosa since much of the dose of an ophthalmic solution will drain from the eye *via* the nasolacrimal duct. Approximately 4-8% of an intranasal dose and 2-3% of an oral dose of nedocromil sodium is absorbed.

Nedocromil sodium is bound reversibly (up to 89%) to human proteins and to a lesser extent in animals. It is not metabolized in man or animals. In man it is excreted unchanged in the

urine (approximately 70%) and in faeces (approximately 30%). While the plasma concentration falls rapidly (i.e. 10% of peak levels in 8 hours) and urinary excretion is 90% within 12 hours, faecal eliminations may take up to 3 days to be completed.

INDICATIONS AND CLINICAL USE

ALOCRITM (nedocromil sodium 2%) ophthalmic solution is indicated for the treatment of seasonal allergic conjunctivitis.

ALOCRITM must be used regularly to ensure optimal control of symptoms.

Treatment with ALOCRITM should be initiated as closely as possible to the start of the symptoms.

ALOCRITM may be used in conjunction with other anti-allergic therapies, including topical ophthalmics, (xylometazoline, naphazoline, sodium cromoglycate) topical nasal solutions (xylometazoline, flunisolide, pseudoephedrine) and systemic therapies eg. (oral antihistamine) as no interactions have been reported.

CONTRAINDICATIONS

Known hypersensitivity to nedocromil sodium, disodium edetate or benzalkonium chloride.

WARNINGS

Patients who use soft contact lenses must not wear them during the treatment period with ALOCRITM (nedocromil sodium) ophthalmic solution. Benzalkonium chloride, a constituent of the formulation, may accumulate in soft contact lenses. This preservative, when slowly released, could possibly irritate the cornea.

In patients who continue to wear hard or gas permeable contact lenses during ALOCRITM treatment, the lenses should be taken out of the eye prior to instillation of the drops. They should be inserted again not earlier than five minutes after administration, in order to allow an even conjunctival distribution of the solution.

To avoid contamination of the contents, patients should not touch the tip of the container or allow the tip of the bottle to come into contact with the eye.

PRECAUTIONS

USE IN ELDERLY

There is no evidence to suggest that a dose reduction in the elderly is required, as 2% nedocromil sodium ophthalmic solution appears to have a similar activity and safety profile in all groups of patient studied with allergic conjunctivitis. However there is limited clinical trial experience with ALOCRITM (nedocromil sodium) ophthalmic solution, in the elderly.

USE IN CHILDREN

The safety and efficacy of ALOCRIL™ in children under three years of age has not yet been established.

USE IN PREGNANCY

Safety in human pregnancy and the absence of adverse effects on the human reproductive process have not been established. Small amounts of nedocromil sodium are known to cross the placenta but without effect in animals. In fact, in reproductive studies, nedocromil sodium at dosage levels up to 100 mg/kg⁻¹ (more than 800 times the human maintenance dose) has shown no teratogenic or embryotoxic effects, nor has it been observed to interfere with reproductive performance, gestation, parturition, or lactation. Nedocromil sodium has not affected male or female fertility nor has it altered the development of progeny.

Although there is no reason to suspect that nedocromil sodium affects the fetus or mother, as with any drug caution must be exercised, especially during the first trimester. The benefits of treatment to the mother must be weighed against the potential risk to the fetus before proposing its use.

NURSING MOTHERS

Safety in breast-fed infants has not been established. Animal studies have indicated no toxicity of nedocromil sodium in suckling newborns receiving drug from the parent or directly by injection. The concentrations of nedocromil sodium in milk of animals were very low but have not been measured in human milk. The benefits of treating a nursing mother must be weighed against potential risk to the infant.

DRUG INTERACTIONS

Nedocromil sodium has been given to man in conjunction with other drugs with no apparent ill-effects. These included ophthalmic solutions such as xylometazoline, antazoline and naphazoline, pheniramine, sodium cromoglycate and dexamethasone; topical nasal therapies, such as xylometazoline, flunisolide, pseudoephedrine, chlorpheniramine and beclomethasone dipropionate, and oral antihistamines such as clemastine, astemizole, diphenhydramine, terfenadine, brompheniramine and promethazine.

Nedocromil sodium by inhalation has also been used with inhaled and oral β_2 -adrenergic agonists, inhaled and oral corticosteroids, theophylline and other methylxanthines and ipratropium bromide. No drug-drug interactions have been observed in humans or in animals.

ADVERSE REACTIONS

No major adverse events associated with ALOCRIL™ (nedocromil sodium) ophthalmic solution have been reported in any of the clinical trials. Only minor adverse effects were reported which were mostly mild and self limiting.

Those adverse events reported with a frequency $\geq 1\%$ in patients who received ALOCRITM in controlled therapeutic trials are displayed in the following table.

Percentage of Patients Reporting Common Adverse Events in Controlled Therapeutic Trials
(AEs reported with a frequency of $\geq 1\%$ for the Total Nedocromil Sodium 2% Group)

ADVERSE EVENT	Total Nedocromil sodium 2% (n= 1552)	Total Placebo (n= 1353)
Headache	10.9	9.3
Eye Burning	7.4*	4.2
Eye Stinging	6.0*	3.1
Taste Perversion	5.4*	0.6
Eye Redness	2.3	1.8
Eye Itching	2.2	3.4
Rhinitis	1.9	2.3
Eye Watering	1.7	1.6
Eye Soreness	1.7	0.9
Pharyngitis	1.7	1.2
URI	1.7	1.1
Photophobia	1.2	1.1

* $p < 0.01$

SYMPTOMS AND TREATMENT OVERDOSE

There have been no reported cases of overdose in humans. Animal studies have not shown evidence of toxic effects of nedocromil sodium even at high dosage. If overdose is suspected, treatment should be supportive and directed to the control of the relevant symptoms.

DOSAGE AND ADMINISTRATION

ALOCRITM (nedocromil sodium) ophthalmic solution must be used regularly to ensure

optimal control of symptoms.

Treatment with ALOCRIL™ should be initiated as closely as possible to the start of the symptoms.

Adults and Children Over 3 years of age

Seasonal Allergic Conjunctivitis - one drop into each eye twice daily.

IMPORTANT: Soft contact lenses must not be worn during the treatment period. Benzalkonium chloride, a constituent of the formulation, may accumulate in soft contact lenses. This preservative, when slowly released, could possibly irritate the cornea.

In patients who continue to wear hard or gas permeable contact lenses during ALOCRIL™ is treatment, the lenses should be taken out of the eye prior to instillation of the drops. They should be inserted again not earlier than five minutes after administration, in order to allow an even conjunctival distribution of the solution.

- To avoid contamination of the contents, do not touch any surface with the tip of the container.

PHARMACEUTICAL INFORMATION

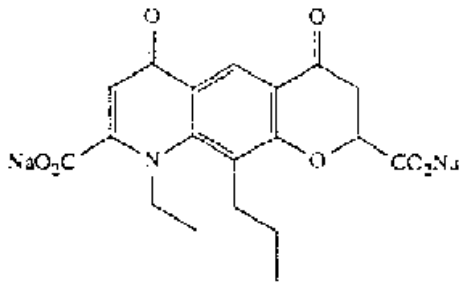
CHEMISTRY

Trade Name: ALOCRIL™

Proper Name: nedocromil sodium 2% (ophthalmic solution)
(U.S.A.N., I.N.N., B.A.N.):

Chemical Name: Disodium 9-ethyl-6, 9-dihydro-4, 6-dioxo-10-
(Drug Substance) propyl-4H-pyrano [3,2-g] quinoline-2, 8-dicarboxylate

Structural Formula:



Molecular Formula: $C_{19}H_{15}O_7NNa_2$

Molecular Weight: 415.3 (disodium salt)

Properties:

Nedocromil Sodium:

Physical form: yellow powder

Solubility: at least 40 mg/ml at 24EC in aqueous buffer (pH 4.4 to 7.4)

pKa values: $pka_1 = 1.0 \pm 0.1$ (pyrone acid)

$pka_2 = 2.5 \pm 0.1$ (quinolone acid)

pH: 5.1 - 7.1 (1% solution in CO₂ free water)

Melting Point: Over 300EC with decomposition

Composition of 2% Ophthalmic Solution

Ingredients	% w/v
Nedocromil sodium	2.0
Benzalkonium chloride	0.01
Disodium edetate	0.05
Sodium chloride	0.547
Purified water	to 100 mL

Stability and Storage Recommendations

Store between 4EC and 25E C . Protect from direct sunlight.

AVAILABILITY OF DOSAGE FORMS

ALOCRITM is a sterile aqueous solution of 2% w/v nedocromil sodium. The solution is made isotonic with 0.547% w/v sodium chloride and preserved and stabilised with 0.01% w/v benzalkonium chloride (BKC) and 0.05% w/v disodium edetate (EDTA).

It is presented as a clear pale yellow liquid in white opaque or translucent polyethylene dropper bottles containing 2.5, 5 or 10 mL.

INFORMATION TO THE CONSUMER

PLEASE READ THIS INSERT CAREFULLY BEFORE STARTING ALOCRITM (NEDOCROMIL SODIUM) AND EVERYTIME YOUR PRESCRIPTION IS RENEWED.

ALOCRITM

nedocromil sodium 2% ophthalmic solution

Therapeutic classification: anti-allergic/anti-inflammatory

ALOCRITM (nedocromil sodium 2%) ophthalmic solution relieves and treats the symptoms of itchy watery red eyes caused by allergies.

About ALOCRITM and Allergies

ALOCRITM is a 2% solution of nedocromil sodium in water and contains benzalkonium chloride and disodium edetate as preservatives. It is useful for the relief and treatment of symptoms caused by allergy in the eye, known as allergic conjunctivitis.

Allergic conjunctivitis results in inflammation of the conjunctiva, the thin, outer, transparent membranes under the eyelids and over the external part of the eyes. This disorder is usually preceded by exposure to allergy-provoking substances in the environment (e.g. tree, grass or weed pollens, mould spores, animal dander and dust). Allergic conjunctivitis is common in the hay fever season.

The symptoms of allergic conjunctivitis are irritation, itchiness, grittiness, soreness, and excessive watering of the eyes. These symptoms are generally accompanied by a stuffy, runny nose (acute allergic rhinitis) commonly known as hay fever.

IMPORTANT: ALOCRITM must be used regularly to ensure optimum control of symptoms. You should start using ALOCRITM as closely as possible to the start of your symptoms.

- **SOFT CONTACT LENSES MUST NOT BE WORN during the treatment period with ALOCRITM. Benzalkonium chloride, a constituent of the formulation, may accumulate in soft contact lenses. This preservative, when slowly released, could possibly irritate the cornea.**

In patients who continue to wear hard or gas permeable contact lenses during ALOCRITM treatment, the lenses should be taken out of the eye prior to instillation

of the drops. They should be inserted again not earlier than five minutes after administration, in order to allow an even conjunctival distribution of the solution.

- To avoid contamination of the contents, do not touch any surface with the tip of the container.
- Store between 4EC and 25E C. Protect from direct sunlight.

Always Remember

Before taking this medication tell your doctor and pharmacist if you:

- are allergic to or have had a reaction to nedocromil sodium, or any of its components, in the past;
- are, or intend to become, pregnant;
- are, or intend to breast feed;
- are taking any other medications, either prescription or non-prescription (over the counter);
- have any other medical problems.

While taking this medication

- Tell any other doctor, dentist or pharmacist, that you consult or see, that you are taking this medication.
- Check with your doctor if you are not getting any relief of your symptoms.
- Report any untoward reaction to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.
- **YOUR REGULAR MEDICAL CHECK UPS ARE ESSENTIAL.**

Precautions

Very little nedocromil sodium is absorbed into the body when using ALOCRITM as directed in the eye.

Along with its benefits, ALOCRITM, like other drugs, may cause some undesirable reactions. Although not all these side effects may occur, if they do occur they may need medical attention. Local side effects in the eye are generally mild and tend to disappear promptly if treatment is stopped.

Check with your doctor if any of the following side effects occur:

- eye irritation (burning or stinging sensation of the eyes)
- headache
- blurred vision
- unpleasant taste

Other side effects not listed may also occur in some patients. If you notice any other effects, check with your doctor.

DOSING

The dose of ALOCRITM may be different for different people.

Adults and Children Over 3 years of Age: The usual dosage is one drop into each eye, twice daily.

Directions for Use

1. Sit down in front of a mirror so that you can see what you are doing.
2. Pull the lower eyelid down gently and then carefully place one drop into the gap between the eye and lower eyelid taking care not to touch the eye with the tip of the bottle.
3. Release the lower eyelid and blink a few times to ensure the whole eye is covered by the liquid.
4. Repeat the process for the other eye.

Missed Dose

Try to take the drops at regular times, to help you remember to take them.

If you miss a dose, take it as soon as you realize the omission; then proceed as normal.

CLINICAL EXPERIENCE WITH PREGNANT WOMEN OR CHILDREN UNDER THREE YEARS OF AGE IS LIMITED.

DO NOT KEEP OUTDATED MEDICINE OR MEDICINE NO LONGER NEEDED. KEEP OUT OF THE REACH OF CHILDREN.

THIS MEDICINE HAS BEEN PRESCRIBED FOR YOUR MEDICAL PROBLEM. DO NOT GIVE IT TO ANYONE ELSE.

IF YOU REQUIRE MORE INFORMATION ON THIS DRUG, CONSULT YOUR DOCTOR OR PHARMACIST.

PHARMACOLOGY

Animal Pharmacodynamics

In Vitro

Bronchoalveolar (BA) cells were recovered by lung lavage from macaque monkeys previously infected with *Ascaris suum*. Approximately 22% of these cells were mast cells, predominantly of the sub-type classified as mucosal mast cells. Nedocromil sodium in micromolar concentrations inhibited the release of histamine and the inflammatory mediators, leukotriene C₄ and prostaglandin D² by 30%, from BA cells when these cells were challenged with specific antigen or with anti-human IgE. Sodium cromoglycate exhibited comparable activity only at concentrations of 10⁻⁴M or higher against challenge with anti-IgE and was essentially inactive against challenge with antigen⁷⁻¹³.

Mast cells recovered from the rat peritoneum are of the connective tissue sub-type. Release of histamine from these cells following a variety of different challenges (including anti-rat IgE) was inhibited equally by nedocromil sodium and sodium cromoglycate at micromolar concentrations⁵⁻⁶.

The mechanism by which nedocromil sodium inhibits mediator release from mast cells is incompletely understood. It does not inhibit Ca⁺⁺ flux nor does it exert any discernible action on two key enzymes in the arachidonic acid cascade: lipoxygenase and cyclo-oxygenase. Nedocromil sodium at concentrations of 10⁻⁷ to 10⁻⁴M appears to induce the phosphorylation of a 78K protein found in rat connective tissue mast cells. It is thought that the phosphorylation of these proteins is associated with the termination of release of mediators. Sodium cromoglycate also induces the phosphorylation of this protein¹⁴⁻¹⁵.

Nedocromil sodium has no effect on the isolated bronchial or ileal smooth muscle of the guinea pig.

Nedocromil sodium inhibits IgE mediated activation of rat platelets and macrophages as measured by anti-schistosome cytotoxicity, oxygen mediated chemiluminescence and macrophage lysosomal enzyme activity¹¹²⁸.

In-Vivo

Nedocromil sodium and sodium cromoglycate were about equally effective in inhibiting peritoneal, passive cutaneous and lung anaphylaxis in the rat. The intravenous ID₅₀ for both compounds was 1 to 2 mg/kg⁻¹ in the latter two tests. Sodium cromoglycate pretreatment blocks the inhibitory response of nedocromil sodium in the rat passive cutaneous anaphylaxis model, suggesting a similar mode of action for the two compounds in blocking the degranulation of rat connective tissue mast cells. From other studies, both compounds appear equally effective when their dose dependent inhibitory actions on rat connective tissue mast cells are compared *in vivo*.

The actions of nedocromil sodium on the respiratory, cardiovascular and autonomic nervous

systems resemble those of sodium cromoglycate⁴¹. Nedocromil sodium does not affect the resting respiratory pattern or bronchial mucus production in the cat. It is not a bronchodilator and does not affect autonomic regulation of the respiratory system. Nedocromil sodium has been shown to induce a vagally mediated depressor response in the dog and a pressor response in the marmoset. These effects appear to be species related as only minimal effects on heart rate and blood pressure were observed in rat, guinea pig, rabbit and cat.

Interaction studies with the antihistamine terfenadine, the α -adrenoceptor agonist xylometazoline, the β -adrenoceptor agonist salbutamol, the phosphodiesterase inhibitor aminophylline, and the anticholinergic agent ipratropium bromide indicate that nedocromil sodium is unlikely to interact adversely with other drugs commonly used in the treatment of allergic conjunctivitis.

Nedocromil sodium has also been shown not to interact with CNS drugs (alcohol or pentobarbitone sodium).

Animal Pharmacokinetics

In Vitro

Radiolabelled [¹⁴C] nedocromil sodium was largely confined to the plasma fraction of whole blood in the rat.

Maximum plasma protein binding was 80% in the rabbit, 72% in the rat, 70% in the dog and 40% in the mouse.

In Vivo

Nedocromil is not metabolised by any species studied and is very rapidly cleared by biliary and urinary excretion. The excretion processes are similar between species, although the relative importance of the two routes differs and the rate of clearance varies inversely in proportion to bodyweight.

Intravenous and Subcutaneous Routes

After subcutaneous administration nedocromil sodium is rapidly and completely cleared from the injection site in rats, rabbits and dogs.

Inhalation and Intranasal Routes

In the rat and dog following administration by the inhalation and intranasal routes, significant systemic absorption occurred (2-76%, depending on route, species and method of administration), although only about 10% of the dose administered by inhalation reaches the site of absorption in the peripheral airways.

Oral Route

Absorption after oral administration to the mouse, dog and man is low and somewhat variable between species about 0.2%-29%, depending on dose and methodology.

Ocular Route

Repeated doses of [¹⁴C] nedocromil sodium over a 24 hour period to the eyes of rabbits, showed that penetration of nedocromil sodium into the eye was low and clearance was rapid. At one hour up to 0.2% of the total dose was associated with all eye tissues, with only 0.006% of the total dose detectable in the internal tissues of the eye at this time. At 24 hours, only 0.017% of the dose remained in or on the eye and adnexa.

Sex Differences

No significant sex differences have been seen in any of the pharmacokinetic studies apart from a slightly higher bile and faecal excretion in female rats. This difference is not considered to be especially important.

Pregnancy

No significant changes in pharmacokinetic behaviour of the nedocromil sodium is seen during pregnancy in rabbits and rats. Maternal distribution of nedocromil sodium in the pregnant rat mirrors the non-pregnant animal. Only low concentrations (0.42 Fg/mL⁻¹ after 5 months and 0.15 Fg/mL⁻¹ after 1 hour) of nedocromil sodium have been detected in rat milk after intravenous injections of 5 mg/kg⁻¹ and less than 2% of the total absorbed dose is likely to be excreted by this route in the rat.

Age Difference

No significant age differences have been seen in pharmacokinetic parameters monitored in mice up to 18 months old.

Human Pharmacodynamics

In Vitro

Early studies have indicated that nedocromil sodium inhibited anti-IgE mediated histamine release from human bronchial mast cells obtained by lavage. Nedocromil sodium was significantly more potent than sodium cromoglycate in this action (IC₃₀ nedocromil sodium 6 x 10⁻⁷ M; IC₃₀ sodium cromoglycate - 10⁻⁵ M).

Nedocromil sodium also inhibited, in a dose-dependent fashion, the expression of the complement C_{3b} receptor on normal human neutrophils and eosinophils. It did not inhibit histamine release from human basophils in response to anti-IgE or antigen challenge. Nedocromil sodium did not interfere with the bactericidal activity of human neutrophils²¹⁻²⁸.

In Vivo

Nedocromil sodium administered in the eyes of 6 healthy human volunteers in single dose of 0.5% (0.2 mg), 1% (0.4 mg) and 2% (0.8 mg) was well tolerated. At a concentration of 4% (1.6 mg), minor events were reported (ocular irritation and distinctive taste). There was no alteration in visual acuity or other objective measurement following any treatment.

Multiple doses included ocular administration of 1% (0.4 mg) and 2% (0.8 mg) four times daily for seven days. No changes were observed in ophthalmoscopy or on other ophthalmological examination during and after treatment.

Human Pharmacokinetics

In Vitro

Radiolabelled [¹⁴C]-nedocromil sodium was largely confined to the plasma fraction of whole blood and was 89% bound to plasma proteins.

In Vivo

A sensitive radio-immunoassay procedure⁴³ has been used to measure plasma and/or urinary excretion of nedocromil sodium following ocular, intravenous, oral and intranasal administration.

Following intravenous infusion, nedocromil sodium was rapidly removed from the circulation (clearance = 10.2 ± 1.3 mL/min/kg). The plasma concentration declined biexponentially with half-lives of 4 and 53 minutes and 81% of the dose was excreted in the urine.⁴⁴ An intravenous dose of [¹⁴C]nedocromil sodium was rapidly excreted, 64% of the dose in the urine and 36% in the faeces; 97% of the total urinary excretion was complete within the first 4 hours dosing.

Intravenous and Subcutaneous Routes

Nedocromil sodium is distributed in the extracellular fluid with little or no CNS penetration and does not accumulate in the body. In man 60% is excreted in urine within 24 hours, the remainder is eliminated in the faeces. Plasma clearance values are high, ranging from 10 mL/kg⁻¹ min⁻¹ in man to greater than 300 mL/kg⁻¹/min⁻¹ in the mouse.

Oral Route

With oral administration of 1 mg/kg⁻¹ a mean peak plasma concentration of 5.8 ng/mL⁻¹ was reached one hour after dosing. An initial rapid decline was followed by a slow fall in plasma concentration, with a half-life of 21 hours. Urinary excretion over 72 hours was incomplete but had accounted for 1.7% of the dose. Hence 2-3% of a dose is estimated to be absorbed by the oral route.

Ocular Route

By the ocular route, absorption of nedocromil was studied in relation to urinary excretion, after a single dose and multiple dose application. In the single dose study, following administration of 0.2, 0.4, 0.8, and 1.6 mg as one drop per eye of 0.5%, 1%, 2% and 4% nedocromil sodium aqueous solutions, the absorption calculated from the data on urinary excretion was approximately 2.8% of the dose. In the multiple dose study, following administration of 0.4 and 0.8 mg four times daily, after seven days, the absorption was 3.6%.

The systemic absorption of nedocromil sodium from eye drops is predominantly by way of the nasal mucosa since clearance from the eye involves drainage through the nasolacrimal canal. It has been shown that the absorption of nedocromil sodium in the nasal mucosa in a single dose application is approximately 4% and in multiple dose 8%. It is estimated that between 2 - 3% of the topical dose was orally absorbed.

The pharmacokinetic profile seen in patients and volunteers was similar. Human and animal pharmacokinetics were also similar.

TOXICOLOGY

Nedocromil sodium toxicology has been evaluated in several laboratory animal species. A large number of controlled, toxicological, reproductive and special studies including tests for carcinogenicity and mutagenicity were carried out.

No significant adverse effects attributable to nedocromil sodium were observed in any of these tests. This low toxicity is confirmed by the absence of local or systemic toxic effects in patients given therapeutic doses continuously for more than one year.

The preclinical tests are relevant for assessing safety in man for the following reasons. Metabolism does not occur in any species including man. Nedocromil sodium is excreted unchanged in bile and urine. The pharmacokinetic profile is comparable in man and laboratory animals.

Acute Toxicity

Single doses of nedocromil sodium up to 4000 mg/kg⁻¹ administered orally and subcutaneously to male rats and mice produced no effects over a 14-day observation period. Single doses of 1000 mg/kg⁻¹ and 500 mg/kg⁻¹ were administered intravenously to mice and rats, respectively, without effect. Mice receiving intravenous doses of 2000 mg/kg⁻¹ showed a slight decrease in spontaneous activity. A similar effect was seen in rats at doses of 1000 mg/kg⁻¹ and 2000 mg/kg⁻¹ intravenously. Intravenous doses of 4000 mg/kg⁻¹ produced rapid death in both species.

Anaesthetized cats showed no effects from intravenous doses of nedocromil sodium up to 240 mg/kg⁻¹.

Nedocromil sodium delivered by pressurized aerosols in concentrations of up to 1650 µg/litre had no significant effect on mice exposed for 1 hour.

Subacute Toxicity

Male Beagle dogs received twice daily intravenous injections of nedocromil sodium for 14 days in doses of 4 mg/kg⁻¹ or 40 mg/kg⁻¹. Transient ataxia lasting for up to 1 minute was observed to occur several times during the first 8 days of treatment in the 2 low dose dogs. In contrast ataxia was only seen to occur on 1 occasion on the first day in 1 of the 2 high dose dogs. This response results from a transient hypotensive reflex which is specific to this species. The response is tachyphylactic and occurs after low doses are administered. Responses to subsequent injections appear to be inhibited by circulating nedocromil sodium. This explains the lower incidence of ataxia in the high dose group. No other untoward effects were found.

Beagle dogs were exposed to nedocromil sodium for 90 days at daily doses of 1 or 6 mg/kg⁻¹ delivered by inhalation from pressurized aerosols. Salivation in response to the aerosol occurred and loose stools were noted in some animals but no other untoward effects were noted. There was no organ or tissue toxicity.

Beagle dogs also received nedocromil sodium intranasally for 6 months at a daily dose of 3 mg/kg⁻¹ or 6 mg/kg⁻¹. No toxicity was seen.

Rats received nedocromil sodium subcutaneously for 34 days at daily doses of 60 mg/kg⁻¹ or 180 mg/kg⁻¹. No organ tissue toxicity or untoward effects were observed.

Rats also received nedocromil sodium intravenously for 28 days at daily doses of 10, 40 or 120 mg/kg⁻¹. No organ or tissue toxicity or ill effects were observed.

Rats were exposed to nedocromil sodium inhalation for three months in daily doses of either 8 mg/kg⁻¹ or 30 mg/kg⁻¹. No effects were seen other than a modest increase in lung macrophages, principally in response to the surfactant excipient in the formulation.

Rabbits received nedocromil sodium intranasally for 28 days at a daily dose of 125 mg/kg⁻¹. No toxicity due to nedocromil sodium was detected.

Ocular Toxicity

Four rabbit studies ranging from a single dose to 6-month continuous daily dosing have been performed using a range of concentrations of nedocromil sodium (1, 2 and 4% solution). In a single dose study in albino rabbits using a 2% solution no ocular irritation was seen. In addition, no ocular effects, including ophthalmoscopy and microscopic examination of the eyes were seen in either a 7-day study (using 1%, 2% and 4% solutions) or a 3-month study (2% and 4% solutions) in pigmented rabbits. Finally, in a 6-month study (1%, 2% and 4% solutions) in albino rabbits, which included pachymetry and tonometry measurements as well as ophthalmoscopy and microscopical examinations, no ocular toxicity was seen. It is considered that the comments about yellow coloration made by technical staff were probably due to variable reflections from the surrounding eye tissues where apparent yellow encrustation was observed in the fur, presumably of nedocromil sodium. No yellow corneal coloration was seen in any other ocular study, nor was it seen in the long term inhalation studies in albino rats. There have been no reports of corneal discoloration following the administration of nedocromil sodium 2% ophthalmic solution in man.

Chronic Toxicity and Carcinogenicity

Rats were exposed to nedocromil sodium inhalation for several hours a day for 6 months at daily average doses of 8 mg/kg⁻¹ or 34 mg/kg⁻¹ and for 2 years at daily doses of 8 mg/kg⁻¹ or 23 mg/kg⁻¹. These animals were compared with groups receiving air alone or the propellants and surfactant. Other than the increase in alveolar macrophages in response to the vehicle there were no untoward effects in these studies. No organ or tissue damage occurred. In the 2-year study, no treatment-related increases in the incidence of tumours was found. Nedocromil sodium by inhalation had no detectable effect on the general health or lifespan of the animals.

Beagle dogs were exposed to repeated daily nedocromil sodium inhalations (25 or 100 aerosol shots per day) for 6 months. Additional animals were used as controls (sham aerosol treatment plus subcutaneous saline) and as a high dose group (100 nedocromil sodium aerosol shots per day supplemented with 2 daily subcutaneous injections of

nedocromil sodium (2 x 100 mg). Thus, the dose levels were approximately 5, 20 and 40 mg/kg⁻¹ or on a dose for dose basis approximately 45, 180 and 360 times the human maintenance dose. Clinical signs that were considered to be related to this vigorous treatment regimen were confined to head shaking and salivation. Two high dose male dogs exhibited clonic convulsions on several occasions. Sometimes the convulsion occurred before dosing. Spontaneous convulsions are relatively common in Beagles and these can be triggered for example by excitement, stress, ataxia and hypotension. It is probable that the convulsions in this study resulted from a combination of a genetic predisposition, the excessive stress of the dosing regimen, high fluorocarbon levels (all factors believed to cause convulsions in dogs) and the transient hypotensive effect of subcutaneous nedocromil sodium (which is a unique activity for nedocromil sodium in this species). All animals survived, and no organ or tissue damage was found.

Since much of an inhaled dose of nedocromil sodium enters the gastrointestinal tract, a second carcinogenicity study in mice was carried out. Daily doses of 20, 60 or 180 mg/kg⁻¹ were incorporated into the diet for 21 months. No toxicity, no effect on survival, no organ or tissue damage and no increased incidence of tumours were found.

Mutagenicity

No evidence of mutagenic potential of nedocromil sodium was found in a complete range of studies with or without metabolic activation. These included *in vitro* tests with *Salmonella typhimurium* (the AMES test), *Saccharomyces cerevisiae*, mouse lymphoma L51787 cells and cultured human lymphocytes. All tests were negative. An *in vivo* micronucleus test in mice at doses of 40, 126 or 400 mg/kg⁻¹ was similarly negative.

Reproduction and Teratogenicity

Nedocromil sodium was administered subcutaneously to male and female rats at daily doses of 10, 30 or 100 mg/kg⁻¹. Males were dosed for at least 63 days before mating. Females were dosed for 14 days before mating and throughout mating, gestation and lactation. No untoward effects of these high doses (up to 800 times the human maintenance dose) were detected in F₀ or F₁ generations. There was no decrease in fertility, reproductive performance or fecundity. There was no interference with gestation, parturition or lactation, or with the development of the offspring and their subsequent fertility.

A similar study in mice with dose levels of 1, 10, or 100 mg/kg⁻¹ which was completed up to examination of foetuses in uterus also provided evidence of the lack of effect of nedocromil sodium on reproductive capacity and foetal development.

Specific tests were carried out in rats (doses of up to 100 mg/kg⁻¹) for the effects of nedocromil sodium during the perinatal and postnatal periods, and during the post-weaning to sexual maturity period. No adverse effects of nedocromil were detected.

Specific teratogenicity tests were also carried out in pregnant rats (10, 30 or 100 mg/kg⁻¹ subcutaneously from day 6 to day 16 of gestation), and rabbits (10, 30 or 100 mg/kg⁻¹ from day 6 to day 18 of gestation). There was no evidence for maternal or fetal toxicity. There was no change in litter parameters, and in the fetuses there was no increase in the soft tissue or

skeletal abnormalities.

Other Toxicity

Nedocromil sodium did not significantly inhibit ciliary motility in rabbit tracheas *in vitro* in concentrations below 25 mg/mL⁻¹. However, at concentrations above 25 mg/mL⁻¹ ciliary beat frequency declined with ciliostasis occurring in 48 hours.

Nedocromil sodium produced no evidence of immune enhancement or immune suppression in special studies or in the standard toxicological tests.

Conclusions from the Toxicology Studies

Nedocromil sodium has a remarkably low order of toxicity as demonstrated in many systems. The safety margins, thus established, give confidence that extended use in humans does not constitute a significant toxicological hazard.

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