

**REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:**

**KEY WORDS:** Ophthalmic, Anti-inflammatory, Anti-allergic, Pyranoquinoline

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**Division Name:** Anti-Inflammatory, Analgesic and Ophthalmoscopic Drug Products

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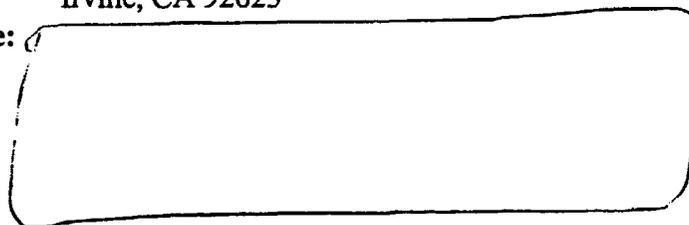
**IND/NDA number:** 21-009

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**Information to sponsor:** Yes (x) No ( )

**Sponsor (or agent):** Allergan, Inc.  
2525 Dupont Drive  
P.O. Box 1934  
Irvine, CA 92623

**Manufacturer(s) for drug substance:**



**Drug:**

**Established Name:** Nedocromil Sodium 2% Ophthalmic Solution

**Code Name:** 8729X, FPL 59002

**Trade Name:** Abrevia

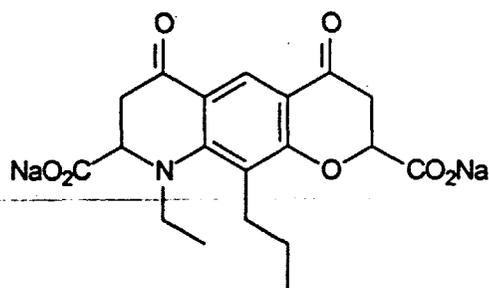
**Chemical Name:** 4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylic acid-9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-, disodium salt

**CAS Registry Number:** 69049-74-7

**Molecular Formula:** C<sub>19</sub>H<sub>15</sub>NNa<sub>2</sub>O<sub>7</sub>

**Molecular Weight:** 415.30

**Chemical Structure:**



**Relevant INDs/NDAs/DMFs:**

IND  
IND  
IND  
IND

DMF

DMF

DMF

**Drug Class:**

Pyranoquinoline, Anti-allergic

**Indication:**

Prevention and treatment of allergic conjunctivitis

**Clinical formulation:**

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

**Previous clinical experience:**

Nedocromil Sodium 2% Ophthalmic Solution has been approved for use in 20 different countries, with the first approval to market in the United Kingdom in 1986. It has not been taken off of the market in any country and a marketing application is pending in South Africa. Clinical trials have been conducted in 1552 patients receiving Nedocromil sodium 2% Ophthalmic Solution up to 4 times per day for up to 12 weeks.

**Route of administration:**

Topical ophthalmic

**Dose:**

1 - 2 drops twice per day (up to 3.2 mg/day)

**Disclaimer:**

Some information in this review may be directly from the Sponsor's submission.

**Studies reviewed within this submission:**

Studies reviewed are pertinent to ophthalmic use and listed in the Review Index.

**Studies not reviewed within this submission:**

Studies submitted and reviewed under previously listed INDs and NDAs were not reviewed.

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APPEARS THIS WAY  
ON ORIGINAL

## **INTRODUCTION AND DRUG HISTORY:**

The Sponsor is pursuing marketing approval for Nedocromil Sodium 2% Ophthalmic Solution for the prevention and treatment of allergic conjunctivitis. Nedocromil sodium is an anti-inflammatory agent in the drug class of pyranoquinolines. Nedocromil sodium is currently approved for market in the United States for the prevention and treatment of asthma. Asthma patients inhale up to 14 mg/day. The dose for Nedocromil Sodium 2% Ophthalmic Solution is 3.2 mg/day. Nedocromil Sodium 2% Ophthalmic Solution is currently approved for market in 20 different countries with the first approval in the United Kingdom in 1986. It has not been taken off of the market in any country and a marketing application is pending in South Africa. Clinical trials have been conducted in the 1552 patients receiving Nedocromil Sodium 2% Ophthalmic Solution up to 4 times per day for up to 12 weeks.

A number of ophthalmic conditions including acute and chronic conjunctivitis, vernal keratoconjunctivitis and giant papillary conjunctivitis are characterized by itchiness, photophobia and mucoid discharge. The association of these diseases with sensitivity to allergens, increased reactivity to non-specific and specific stimuli and accumulation of inflammatory cells are similar to those found in nasal allergy and asthma.

The pathophysiology of allergic ophthalmic conditions is initiated by the release of mediators from inflammatory cells including mast cells, neutrophils, eosinophils and monocytes. A sequence of events leading to a local inflammatory response, and to some extent a self-perpetuating reaction in the eye, would be as follows: antigen-induced mediator release from epithelial mast cells in the conjunctiva and eye lids, release of pro-inflammatory mediators, accumulation of inflammatory cells producing local inflammation and tissue damage with increased hyperresponsiveness and secretion of tears.

Many of the pharmacology and toxicology studies used to demonstrate the safety of Nedocromil Sodium

Additional studies submitted to support the safety of topical ophthalmic use of Nedocromil sodium are listed in the review index and are reviewed herein. The primary focus of this review is the safety of ophthalmic dosage form of Nedocromil sodium.

## **PHARMACOLOGY:**

### Mechanism of Action:

The following information regarding the pharmacologic action of Nedocromil Sodium, included in the label for Tilade® inhaler, is also relevant for the ophthalmic dosage form.

Nedocromil sodium has been shown to inhibit the *in vitro* activation of, and mediator release from, a variety of inflammatory cell types associated with asthma, including eosinophils, neutrophils, macrophages, mast cells, monocytes, and platelets. *In vitro* studies on cells obtained by bronchoalveolar lavage from antigen-sensitized macaque monkeys show that Nedocromil sodium inhibits the release of mediators including histamine, leukotriene C<sub>4</sub>, and prostaglandin D<sub>2</sub>. Similar studies with human bronchoalveolar cells showed inhibition of histamine release from mast cells and beta-glucuronidase release from macrophages.

#### Drug Activity Related to Proposed Indication:

Atopic patients with conjunctivitis are sensitive to a range of common antigens and produce a local Type I immediate hypersensitivity reaction following ocular challenge with antigen. This immune reaction is initiated by the specific interaction of antigen and membrane-bound antibody on the mast cell, and potent pharmacological substances released from a variety of inflammatory cells including mast cells and eosinophils mediate the characteristic sequence of pathological events.

The immune system activation and degranulation of mast cells is likely to be responsible for the acute effects of exposure to antigen in allergic eye disease. The later chronic inflammatory state, however, depends on the activation of other cell types such as eosinophils and epithelial cells.

Structures of the eye that are in contact with external environment are well supplied with mast cells.<sup>1</sup> Ninety-four percent of mast cells are found in the conjunctiva and lids of both rats and man.<sup>2</sup> Levels of mast cell-derived mediator, histamine, are raised significantly in the tears of patients with vernal keratoconjunctivitis.<sup>3</sup> In addition, topical challenge with histamine phosphate in normal volunteers produces the acute symptoms of conjunctivitis.<sup>4</sup> Although mast cells are rarely seen in the normal conjunctival epithelium, there is an increase in the numbers of tryptase-chymase positive mast cells (MC<sub>TC</sub>) (equivalent to connective tissue mast cells) in vernal conjunctivitis with a smaller increase in numbers of tryptase-alone staining mast cells (mucosal mast cells) in the epithelium in this condition.<sup>5</sup> A characteristic of ocular allergy is the accumulation of eosinophils.<sup>6, 7</sup> and it is known that products released following eosinophil activation

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<sup>1</sup> Allansmith, M.R. 1978. Number of inflammatory cells in the normal conjunctiva. *Am J Ophthalmol.* 86:250-259.

<sup>2</sup> Allansmith, M.R. et al. 1979. Mast cells in ocular tissues of normal rats and rats infected *Nippostrongylus brasiliensis*. *Invest Ophthalmol Vis Sci.* 18(8):863-867.

<sup>3</sup> Sharma, P. and Gupta S.K. 1985. Clinical and pharmacologic evaluation of disodium chromoglycate in the management of vernal keratoconjunctivitis. *ICTS Med Sci* 13:857-858.

<sup>4</sup> Abelson, M.B. 1977. Histamine in human tears. *Am J. Ophthalmol.* 83:417-418.

<sup>5</sup> Irani, AMA et al. 1990. Human conjunctival mast cells: Distribution of MC<sub>T</sub> and MC<sub>TC</sub> in vernal conjunctivitis and giant papillary conjunctivitis. *J All Clin Immunol* 103:1198-1199.

<sup>6</sup> Friedlander, M.H., et al. 1984. Diagnosis of allergic conjunctivitis. *Arch Ophthalmol.* 103:1198-1199.

have the potential for causing tissue damage.<sup>8</sup> Recently, it has been recognized that the epithelium is not simply a barrier but, following activation of epithelium, several cytokines and growth factors capable of maintaining the inflammatory response are released.<sup>9</sup>

The allergic response in the eyes of antigen-induced rodents was suppressed after treatment with Nedocromil sodium. *In vivo* studies regarding pharmacologic actions in the eye are summarized in the following table.

Study	Active Sensitization		Passive Sensitization		Reference
	Dose (route)	% Inhibition	Dose	% Inhibition	
Anaphylactic responses in the conjunctiva of Wistar Rats (n=15 males/group)	2 mg/kg (iv) 20 mg/kg (iv) 1.2 mg (topically) 3.0 mg (topically)	33.5 Inactive Inactive Inactive	2 mg/kg (iv)	98.5	FSS1 Fisons Sept. 1987
Anaphylactic responses in the conjunctiva of Duncan Hartley Guinea Pigs (n=5 males/group)			2 mg (topically)	↓ hyperemia and edema ↓ eosinophil counts in limbus, fornix and eyelids	R42E Fisons Oct. 1992
Allergic conjunctivitis in Duncan Hartley Guinea Pigs (n=10 females/group)	20µl of 2% solution (topically)	32.6% of vascular permeability			T26A Fisons Oct. 1993

Several *in vitro* studies were conducted to ascertain the pharmacologic activity of Nedocromil sodium for use in the eye. These studies are summarized in the following table.

Study	Dose	Results	Reference
Mediator release from rat peritoneal mast cells challenged with anti-IgE, Compound 48/80, and Calcium ionophore	$10^{-8}$ - $10^{-4}$ M	IC <sub>50</sub> (M) (histamine release): Anti-IgE: $1.4 \times 10^{-6}$ 48/80: $2.0 \times 10^{-6}$ Ca ionophore: $3.3 \times 10^{-6}$ Maximum inhibition: 30%	SD 4502, 45-6, and 4638, Fisons 7/84, 8/84, and 11/84
Cytokine release from rat peritoneal mast cells	$10^{-5}$ - $10^{-3}$ M	Maximum inhibition: 29.8% at $10^{-3}$ M after 6 h pre-incubation	R86B Fisons 12/91

<sup>7</sup> Bonini, Se et al. 1990. Allergen dose response and late symptoms in a human model of ocular allergy. *J All Clin Immunol* 86:869-876.

<sup>8</sup> Frigas S.E. et al. 1980. Cytotoxic effects of the guinea pig eosinophils major basic protein on tracheal epithelium. *Lab Invest.* 42:35-43.

<sup>9</sup> Soloperto, M. et al. 1991. A bronchial epithelial cell-derived factor in asthma that promotes eosinophil activation and survival as GM-CSF. *Am J. Physiol.* 260:L530-L538.

Study	Dose	Results	Reference
Mediator release from monkey lung lavage cells challenged with IgE	$10^{-7} - 10^{-4}$ M	IC <sub>30</sub> (M) Histamine release: $5.4 \times 10^{-6}$ LTC <sub>4</sub> : $1.3 \times 10^{-6}$ PGD <sub>2</sub> : $1.3 \times 10^{-6}$	SD 4501, 4921, and 4922, 7/84, 8/85, and 8/85
Mediator release from monkey lung lavage cells challenged with antigen	$10^{-7} - 10^{-4}$ M	IC <sub>30</sub> (M) Histamine release: $2.1 \times 10^{-6}$ LTC <sub>4</sub> : $2.3 \times 10^{-6}$ PGD <sub>2</sub> : $1.9 \times 10^{-6}$	SD 4923, 4921, and 4922, 8/85, 8/85, and 8/85
Mediator release from human lung lavage cells (sarcoid diagnostics) challenged anti-IgE	$10^{-9} - 10^{-4}$ M	IC <sub>30</sub> (M) Diagnostic: $6.1 \times 10^{-7}$ Sarcoid: $5.5 \times 10^{-7}$	SD 4755/2, UCL, 7/86
Mediator release from enzyme dispersed human lung tissue cells (carcinoma) challenged with anti-IgE	$10^{-9} - 10^{-4}$ M	IC <sub>30</sub> (M) $7.2 \times 10^{-7}$	SD 4755/2, UCL, 7/86
Mediator release from basophils (human volunteers) challenged with anti IgE or antigen	$10^{-6} - 10^{-3}$ M	No effect	SD 4505, 8/84
Conversion to low density phenotype and mediator release from human eosinophils (normal and atopic subjects) challenged with conditioned medium and calcium ionophore	$10^{-7} - 10^{-5}$ M	Significant inhibition of low density eosinophil formation induced by conditioned medium  Significant inhibition of LTC <sub>4</sub> generation by ionophore at $10^{-6} - 10^{-5}$ M  No effect on superoxide generation by ionophore	Sedgwick, J.B. et al. 1992. J All Clin Immunol 90:202-209.
Activation of human eosinophils by fMLP	$10^{-10} - 10^{-5}$ M	IC <sub>30</sub> (M) C3b receptor expression: $1.2 \times 10^{-9}$ IGG1 Fc: $4.5 \times 10^{-10}$ Schistosome killing: max. inhibition - 100% at $10^{-7}$ M	SD 4918 BH 8/85
Chemotaxis of human eosinophils by PAF, LTB <sub>4</sub> , and ZAS	$10^{-9} - 10^{-5}$ M	IC <sub>30</sub> (M) PAF: $1.3 \times 10^{-6}$ LTB <sub>4</sub> : $9.4 \times 10^{-8}$ ZAS: inactive	Bruijnzeel PLB et al. 1990 Br. J. Pharmacol 99(4):798- 802)
Release of GM-CSF from human bronchial epithelial cells	$10^{-7} - 10^{-5}$ M	Dose related inhibition Mac. 43.9% at $10^{-5}$ M	Marini, M. 1992. Pulmon. Pharmacol 5(1):61-65
Release of 15-HETE from human bronchial epithelial cells challenged with toluene diisocyanate	$2.2 \times 10^{-12} - 2.2 \times 10^{-6}$ M	Dose related inhibition of 15-HETE release (48% at $2.2 \times 10^{-8}$ M)	Mattoli, S. et al. 1990. Int Arch Allergy Appl Immunol 92(1):16-22

In addition to pharmacology studies designed to study the ophthalmic use of Nedocromil sodium, studies to elucidate the immunologic properties of the drug have been conducted. These studies have been previously submitted and reviewed, and pertinent information from them is included in the label for Tilade® (reproduced above).

Interestingly, the mechanism of action of Nedocromil sodium has not been fully identified. Using the rat peritoneal mast cell model of cell activation, studies have shown that the compound prevents the release of mediators by modulating a signal transduction system. Further evidence of the effect of the compound at this level comes from the work demonstrating that Nedocromil sodium inhibits the activation of neutrophils stimulated by phorbol ester. However, as the physical chemical properties of Nedocromil sodium make it unlikely that the compound can enter the cells, it is reasonable to speculate that Nedocromil sodium modifies second messenger systems by interacting with a yet unidentified surface receptor.

#### Summary of Pharmacology:

The *in vivo* studies demonstrate that Nedocromil sodium suppresses the allergic response in the eye of rodents. The compound was shown to suppress a range of symptoms including erythema, edema, and cell accumulation. These results may be explained by the ability of Nedocromil sodium to inhibit the activation of cells involved in the initiation and maintenance of the acute and chronic symptoms of ocular allergy in the *in vitro* studies.

Although the exact mechanism of action of Nedocromil sodium is not known, studies have shown that the compound does not dilate smooth muscle, and it is neither an antagonist nor enzyme inhibitor of mediators believed to be responsible for the symptoms of ocular allergy.

#### **SAFETY PHARMACOLOGY:**

The results of safety pharmacology studies are summarized by organ system tested below. \_\_\_\_\_

#### Neurological effects:

In a battery of general pharmacology tests (SE 7292) designed to investigate potential effects on the central and peripheral nervous systems, intravenously administered Nedocromil sodium up to 10 mg/kg had no effect on central nervous system parameters of behavior in the rat, spontaneous motor activity in the mouse, or body temperature in the rabbit. In addition, Nedocromil sodium given subcutaneously for 7 days at a dose of 100 mg/kg/day had no effect on neuromuscular coordination in mice (SE 6454) or on behavior of rats in a novel open field environment (SE 6453 and SE 6510).

Cardiovascular effects:

Cardiovascular responses to Nedocromil sodium vary with species. No effects or only minor effects were seen on heart rate and blood pressure of anesthetized rabbits and cats (SE 5319 and SE 5981). This was also the case for anesthetized rats and guinea pigs (SD 4282 and SD 4689) after intravenous administration of Nedocromil sodium. In the dog, Nedocromil sodium produces a dose dependent depressor response (SD 4314, SD 4681 and SD 4682) at low doses ( $ED_{50}$  of about 1  $\mu\text{g}/\text{kg}$ ).

Blood pressure and heart rate effects of Nedocromil sodium have also been investigated in conscious male beagle dogs following repeated subcutaneous doses (100 mg/animal/day) over 14 days (SE 6345). Pronounced falls in blood pressure (of up to 80%) and heart rate were seen within two minutes. This response was essentially the same on each of the 14 days. Initial clinical observations included rigidity, emesis, urination and salivation but these declined during treatment until only 'lip-licking' was evident during the two weeks. Decreasing the interval between repeat administration of Nedocromil sodium to 3 hours, but not 6 hours and greater, produced almost complete abolition of the blood pressure response indicating a degree of tachyphylaxis. It was therefore expected, for example, that in the six-month subcutaneous dog study (SE 5805) the first injection of each day would cause a profound blood pressure fall, but not with the second injection given within a few hours of the first dose. This type of response in the dog has been shown to be due to stimulation of the Bezold-Jarish reflex.

In contrast to the response in the dog, intravenous Nedocromil sodium produces a dose-related increase in blood pressure and heart rate in anesthetized marmoset. The response is likely to be due to release of noradrenaline and is subject to tachyphylaxis (SD 4422).

Pulmonary effects:

No significant effect on the respiratory pattern or on the autonomic regulation of the respiratory system was noted in anesthetized cats after intravenous administration over a wide range of doses (SD 4423, SD4690, SD 4522, and SE 5319).

Renal effects:

Nedocromil sodium at 10 mg/kg or less did not affect urine volume or excretion of electrolytes in the mouse, rat and rabbit (SE 7292). The absence of any significant effect on these parameters was confirmed in the repeat-dose studies on this compound.

Gastrointestinal effects:

Nedocromil sodium had no effect of charcoal meal transport on the mouse at doses up to 10 mg/kg (SE 7292). No effects on the gastrointestinal system have been seen in the repeat-dose toxicity studies, other than salivation, emesis and defecation seen in some of

the dog studies which is considered to be due to the pharmacological action of the compound specific to this species.

Summary and Conclusion for Safety Pharmacology:

Nedocromil sodium was tested for possible adverse effects on the central nervous, cardiovascular, respiratory, renal and gastrointestinal systems. No apparent risks of side effects attributable to pharmacologic effects of Nedocromil sodium were revealed in the submitted studies.

**PHARMACOKINETICS/TOXICOKINETICS:**

Systemic exposure to Nedocromil sodium is very low following ocular administration. The pharmacokinetic properties of Nedocromil sodium have been previously studied and submitted [redacted] Additional studies, specific to ophthalmic use, were submitted to the current NDA and are reviewed herein.

PK parameters:

The study summarized below describes the pharmacokinetic parameters of Nedocromil sodium after administration in the eye of rats.

STUDY IDENTIFICATION

*SE 9058 Pharmacokinetics of <sup>14</sup>C-FR107625 (Nedocromil) after Topical Administration to the Eye of the Rat (v6 p248)*

<b>Study Title:</b>	Pharmacokinetics of <sup>14</sup> C-FR107625 (Nedocromil) after Topical Administration to the Eye of the Rat (v6 p248)
<b>Sponsor Study No.:</b>	SE 9058
<b>Study Dates:</b>	Not stated
<b>Report Date:</b>	March 1993
<b>Test Facility:</b>	[redacted] Address not provided
<b>GLP Status:</b>	Not stated

METHODS

<b>Test Article:</b>	<sup>14</sup> C-FR107625 (Nedocromil) (40 mg/ml)
<b>Batch No:</b>	Not stated
<b>Purity:</b>	Not stated
<b>Vehicle:</b>	Sodium chloride (1.3 mg), disodium edetate (0.25mg), benzalkonium chloride (0.05%), and water

<b>Species/Strain:</b>	Rat/Sprague Dawley
<b>No. of Animals:</b>	3/males/group
<b>Route:</b>	Topical ophthalmic
<b>Dosage (mg):</b>	0.4/rat
<b>Treatment Schedule:</b>	Single dose
<b>Observations:</b>	<ul style="list-style-type: none"><li>• Radioactivity concentration in plasma, urine and feces</li><li>• Blood samples were obtained at 5, 15 and 30 minutes and 1, 2, 4, and 6 hours post dose</li><li>• Urine was collected at 0-4, 4-8, 8-24, 24-48, and 48-72 hours post dose</li><li>• Feces were collected at 0-24, 24-48, and 48-72 hours post dose</li><li>• Radioactivity in the gut and carcass was also measured after urine and feces collection</li></ul>

## RESULTS

### **Plasma concentration:**

The plasma concentration of radioactivity reached a peak at 15 minutes after administration and declined rapidly, with a half-life of 20 minutes. Mean plasma concentrations of radioactivity over time are summarized in the following table.

Concentration of Radioactivity (ng/ml equivalents)  
After Ophthalmic Administration of Nedocromil sodium at 0.4 mg/rat

<u>Time After Dosing</u>	<u>Mean ± S.D.</u>
5 min.	55.58 ± 15.07
15 min.	81.51 ± 14.37
30 min.	44.72 ± 12.97
1 h	13.99 ± 1.70
2 h	1.96 ± 0.98
4 h	1.13 ± 1.13
6 h	0.00 ± 0.00

### **Excretion:**

Most (86.2%) of the radioactive dose was excreted in the feces with a much smaller amount (5.7%) excreted in the urine. Nearly the entire radioactivity excreted in the feces and urine was attributable to unchanged Nedocromil. The excretion of Nedocromil sodium over time is summarized in the following table.

Mean Percent Recovery  
After Ophthalmic Administration of Nedocromil sodium at 0.4 mg/kg

<u>Time After Dosing (hr)</u>	<u>Mean ± S.E.</u>
Urine	
0-4	2.04 ± 0.66
4-8	1.09 ± 0.33
8-24	0.96 ± 0.03
24-48	1.30 ± 0.58
48-72	0.28 ± 0.06
0-72 (total urine)	5.67 ± 0.62
Feces	
0-24	68.96 ± 4.69
24-48	15.22 ± 1.19
48-72	1.98 ± 0.71
0-72 (total feces)	86.17 ± 3.01
Cage Wash -- 72	1.16 ± 0.40
Gut -- 72	0.34 ± 0.08
Carcass -- 72	0.77 ± 0.03
Total recovery	94.11 ± 2026

**Key Study Observations:**

Nedocromil sodium has a half-life of 20 minutes in rat plasma and is primarily excreted in the feces (86.2%) with a lesser amount excreted in the urine (5.7%) of rats after topical ophthalmic administration.

**Absorption:**

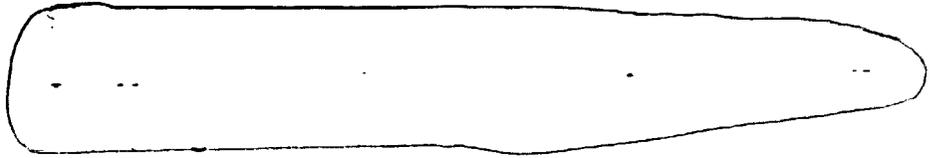
The study summarized below describes the absorption properties of Nedocromil sodium after instillation into the eye of rabbits.

**STUDY IDENTIFICATION**

*SE 6429/1: Ocular Absorption after Topical Administration to the Eye of the Rabbit (v6 p371)*

**Study Title:** Ocular Absorption after Topical Administration to the Eye of the Rabbit  
**Sponsor Study No.:** SE 6429/1  
**Study Dates:** October 1985  
**Report Date:** September 1, 1992

Test Facility:



GLP Status:

Not stated

### METHODS

**Test Article:**  $^{14}\text{C}$ -FPL 59002 (16 mg)  
**Batch No:** B142.124.1 and 1087L  
**Purity:** Not stated  
**Vehicle Control:** Sodium chloride (10.9 mg), disodium edetate (2 mg), and distilled water  
**Species/Strain:** Old English Rabbits (selected for its large pigmented eye and associated conjunctival sac)  
**No. of Animals:** 6 males  
**Route:** Ophthalmic instillation in the conjunctival sac  
**Dosage:** 2 mg  
**Dose Volume ( $\mu\text{l}$ ):** 50  
**Concentration:** 4% w/v solution  
**Treatment Schedule:** Every 2 hours for a total of 4 instillations within a 24 hour period  
**Observations:** The following parameters were evaluated:

- Blood, Plasma, and Tissue Concentration (1, 6, and 24 hours after the last dose). Muscle tissue (i.e., muscle, nictitating membrane, connective tissue), aqueous humor, cornea, lens, vitreous humor, and eyeball (retina, choroid, sclera, ciliary body and iris) were separated and levels of radioactivity were measured.

### RESULTS

#### **Blood, Plasma, and Tissue Concentration:**

The results demonstrate the penetration into the eye was low and clearance from the eye was rapid. At one hour after the last dose a maximum [redacted] of the total dose administered was present in the sum of all eye tissues. Also at one hour after the last dose, only  $0.006 \pm 0.004\%$  of the total dose was associated with the *internal* tissues of the eye. The radioactive material associated with the eye was rapidly cleared; only  $0.019 \pm 0.006\%$  was present in the sum of all eye tissues at 24 hours after the last dose. Mean tissue concentrations are summarized in the following table.

Mean Tissue Concentration ( $\mu\text{g/g}$ )  $\pm$  SD (equivalent to [ ] 59002)  
Following Repeated Administration of 4%  $^{14}\text{C}$ -[ ] 50992 Solution

Tissue	Hour After Last Dose		
	1	6	24
Blood ( $\mu\text{g/ml}$ )	0.207 $\pm$ 0.022	0.066 $\pm$ 0.042	0.031 $\pm$ 0.007
Plasma ( $\mu\text{g/ml}$ )	0.386 $\pm$ 0.012	0.110 $\pm$ 0.114	0.051 $\pm$ 0.001
Muscle tissue	26.4 $\pm$ 30.5	2.31 $\pm$ 1.64	0.923 $\pm$ 0.424
Aqueous humor	2.01 $\pm$ 1.59	0.407 $\pm$ 0.231	0.045 $\pm$ 0.050
Cornea	13.3 $\pm$ 10.8	3.58 $\pm$ 2.34	0.938 $\pm$ 0.802
Lens	0.122 $\pm$ 0.120	0.013 $\pm$ 0.004	0.012 $\pm$ 0.008
Vitreous humor	0.041 $\pm$ 0.025	0.005 $\pm$ 0.002	0.001 $\pm$ 0.001
Eye ball	3.45 $\pm$ 2.56	0.741 $\pm$ 0.515	0.429 $\pm$ 0.238

### Key Study Observations:

Under the conditions of this study, penetration of  $^{14}\text{C}$ -[ ] 50992 into the eye was low and clearance from the eye was rapid.

### Distribution:

The study summarized below describes the distribution properties of Nedocromil sodium after instillation into the eyes of rats.

### STUDY IDENTIFICATION

*SE 9381: Whole-body autoradiographic studies in the distribution of radioactivity after topical administration of  $^{14}\text{C}$ -[ ] 107625 (Nedocromil) to the eye of rats (v 7 p380)*

**Study Title:** Whole-body autoradiographic studies in the distribution of radioactivity after topical administration of  $^{14}\text{C}$ -[ ] 107625 (Nedocromil) to the eye of rats

**Sponsor Study No.:** SE 9381

**Study Dates:** Not stated

**Report Date:** September 1993

**Test Facility:** [ ]

**GLP Status:** Not stated

### METHODS

**Test Article:**  $^{14}\text{C}$ -[ ] 107625 (Nedocromil) (20 mg)

**Batch No:** Code 2347

**Purity:** Not stated

**Vehicle Control:** Sodium chloride (1.3 mg), disodium edetate (0.25 mg), benzalkonium chloride (105µl), and distilled water  
**Species/Strain:** Sprague Dawley Rat  
**No. of Animals:** 7  
**Route:** Topical ophthalmic  
**Dose Volume (µl):** 10  
**Concentration:** 40 mg/ml  
**Treatment Schedule:** Single dose  
**Observations:** The following parameters were evaluated:

- Autoradiography ( 5 and 15 minutes, 1, 6, 24, 48 and 72 hours after dosing)

## RESULTS

### **Autoradiography:**

The presence of <sup>14</sup>C-107625 (Nedocromil) was scored on a scale of 0 (not measurable) to 5 (very high) based on the density of "gray levels" present in the autoradiograms. At five minutes post dosing, very low levels (Grade 0 –1) were detected in the hardierian gland and nasal mucosa. High levels (up to Grade 5) of radioactivity were detected in the eye capsule at 5 minutes post dose, subsided to a very low (Grade 1) level by 1 hour post dose and were not detectable by 24 hours post dose. A very high level (up to Grade 5) of radioactivity was noted in the contents of the stomach and intestines beginning at 1 hour post dose. Lower levels (Grades 0 – 4) were still detectable in the stomach at 24 hours but were not present at 48 hours. A very low level (Grade 1) of radioactivity was evident only in the large intestine at 72 hours post dose.

### **Key Study Observations:**

Radioactivity was present in the eye immediately after dosing and subsided to a very low level by 1 hour post dose and was not present in the eye at 24 hours. A very low level of radioactivity persisted in the large intestine until the 72-hour post dose observation.

### **Metabolism:**

Metabolites of Nedocromil sodium have not been found in urine, feces, or plasma in animal studies previously reviewed under NDA 19-660. This result is consistent with studies in humans where a similar lack of metabolism was found after intravenous dosing (SD 10408).

### Elimination:

Elimination of Nedocromil sodium was studied in rats, as reported in the "PK parameters" section above. Most (86.2%) of the radioactive dose was excreted in the feces with a much smaller amount (5.7%) excreted in the urine. Nearly the entire radioactivity excreted in the feces and urine was attributable to unchanged Nedocromil. This finding is also similar to results found in humans, in that Nedocromil sodium was excreted unchanged via the urine (64%) and bile (36%), however urine:biliary ratios vary widely among species.

### Summary:

Nedocromil sodium plasma levels reached a peak at 15 minutes (81.51 ng/ml) and declined to non-detectable levels by 6 hours in the rat after ocular instillation of 0.4 mg/kg. Nedocromil sodium was excreted unchanged in the feces and urine of rats, with a total recovery of 94.11% of the radioactive dose within 72 hours. Autoradiography in the rat revealed radioactivity in the eye immediately after dosing, which subsided to a very low level by 1 hour post dose and was not present in the eye at 24 hours. A very low level of radioactivity persisted in the large intestine until the 72-hour post dose observation.

Previous studies<sup>10</sup> have shown that Nedocromil sodium is poorly absorbed from the gastrointestinal tract, with 0.2 to 11% oral bioavailability in mouse, 1 to 8% in rat, and 28% in dog. After intravenous administration, tissue distribution of Nedocromil sodium is mainly in the blood, kidney, liver and intestinal tract. Studies show that Nedocromil sodium, when administered intravenously to pregnant rats, is distributed at low levels in the fetal liver and yolk sac and is excreted in milk ( $C_{max} = 1 \mu\text{g/ml}$  at 25 minutes after a 5 mg/kg dose, SE 9147) when administered intravenously to lactating rats. Low levels of Nedocromil sodium were detected in rat milk up to 48 hours after dosing. Plasma protein binding of Nedocromil sodium varies widely among species, at a concentration of 1  $\mu\text{g/ml}$  binding averaged 34% for mouse, 69% for rat, 72% for rabbit, 50% for dog and 82% for human. Nedocromil sodium is excreted unchanged and no metabolites have been identified in mouse, rat, rabbit, or dog. Nedocromil is rapidly eliminated from plasma with clearance rates of  $>300 \text{ ml/min/kg}$  in mouse, approximately 70 ml/min/kg in rat, approximately 20 ml/min/kg in rabbit, and approximately 30 ml/min/kg in dog. The major route of excretion varies among species with a ratio of urinary:biliary percent excretion of 30:70 in mouse, 45:55 in rat, 95:5 in rabbit, and 60:40 in dog. The species with higher proportion of biliary excretion (mouse and rat) have more rapid clearance than the species with higher proportion of urinary excretion (rabbit and dog).

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<sup>10</sup> Submitted and reviewed under NDA 19-660.

## TOXICOLOGY:

### Toxicology studies with Nedocromil sodium

Studies have been conducted in rats, mice, dogs, rabbits and marmosets. The duration of dosing has ranged from a single dose in several species to 2-year carcinogenicity studies in mice and rats. Acute toxicity has been evaluated by oral, intravenous, subcutaneous, inhalation, and ocular routes. Repeat-dose studies have been conducted in mice, rats, dogs, and rabbits via oral, inhalation, intravenous and subcutaneous routes of administration for up to 21 months by the oral route (mouse carcinogenicity) and 24 months by inhalation (rat carcinogenicity). Ocular studies designed to ascertain local and systemic toxicity have been conducted in rats and rabbits for up to 6 months. Given the intended indication for the current NDA, and the fact that studies by other routes of administration have been the subject of previous reviews, the scope of this review is limited to ocular irritation and toxicity studies. Ophthalmic studies were conducted in animals using up to 4% Nedocromil sodium, which is twice the clinical dosage concentration.

### Acute Toxicity

Two acute ophthalmic toxicity studies were submitted to the current NDA and are summarized below.

### STUDY IDENTIFICATION

*SE 5073: Preliminary Eye Irritancy Study in the Rabbit (v6 p 380)*

<b>Study Title:</b>	Preliminary Eye Irritancy Study in the Rabbit
<b>Sponsor Study No.:</b>	SE 5073
<b>Study Dates:</b>	January 1980
<b>Report Date:</b>	January 22, 1980
<b>Test Facility:</b>	

**GLP Status:** Compliant with FDA and OECD GLPs

### METHODS

<b>Test Article:</b>	59002KP (2%)
<b>Batch No:</b>	492H
<b>Purity:</b>	Not stated
<b>Vehicle Control:</b>	Sodium chloride injection
<b>Species/Strain:</b>	New Zealand White Rabbits
<b>No. of Animals:</b>	3 males

**Route:** Topical ophthalmic (one eye per animal)  
**Dose Volume (ml):** 0.1  
**Concentration:** 20 mg/ml  
**Treatment Schedule:** Single dose  
**Observations:** The following parameters were evaluated:

- Ocular examination scored according to Draize (1, 6, 24, 48, 72 hours and 4 and 7 days after instillation)

## RESULTS

### **Ocular Examinations:**

No remarkable observations were noted.

### **Key Study Observations:**

The 2%  59002KP solution was non-irritating to the rabbit eye under conditions of this study.

## STUDY IDENTIFICATION

*SE 6058: Pressurised Aerosol Eye Irritancy in the Rabbit (v6 p390)*

**Study Title:** Pressurised Aerosol Eye Irritancy in the Rabbit  
**Sponsor Study No.:** SE 6058  
**Study Dates:** February 1984  
**Report Date:** May 4, 1984  
**Test Facility:**

**GLP Status:** Compliant with FDA GLPs

## METHODS

**Test Article:**  59002KP in pressurised aerosol cans  
**Batch No:** P1715  
**Purity:** Not stated  
**Vehicle Control:** Water  
**Species/Strain:** New Zealand White Rabbits  
**No. of Animals:** 6 males  
**Route:** 10 metered doses in succession as an aerosol spray into the eye (one eye per animal)

**Dose Volume (ml):** 0.1  
**Concentration:** 44 mg/ml  
**Treatment Schedule:** Single dose regimen  
**Observations:** The following parameters were evaluated:

- Ocular examination scored according to Draize (1, 6, 24, 48, 72 hours and 4 and 7 days after treatment)

## RESULTS

### **Ocular Examinations:**

No remarkable observations were noted.

### **Key Study Observations:**

The 4%  59002KP aerosol was non-irritating to the rabbit eye under conditions of this study.

### Repeated Dose Toxicity:

Repeated dose toxicity was evaluated in 7-day, 3-month, and two 6-month studies in rabbits, which are summarized below.

## STUDY IDENTIFICATION

*SE 6558: Seven-Day Toxicity Study in Rabbits (v6 p 401)*

**Study Title:** Seven-Day Toxicity Study in Rabbits  
**Sponsor Study No.:** SE 6558  
**Study Dates:** December 1984  
**Report Date:** January 25, 1985  
**Test Facility:**

**GLP Status:** Compliant with FDA GLPs

## METHODS

**Test Article:**  59002KP  
**Batch No:** 1708P  
**Purity:** Not stated  
**Vehicle Control:** Sodium chloride in citrate buffer and distilled water

**Species/Strain:** Old English Rabbit (a strain with pigmented eyes)  
**No. of Animals/group:** 3 males  
**Route:** Topical ophthalmic (one eye per animal)  
**Dose Volume :** One drop  
**Concentration:** 1, 2, and 4% for Groups 1,2, and 3, respectively  
**Treatment Schedule:** Four times daily (at approximate 2 hour intervals) for 7 days  
**Observations:** The following parameters were evaluated:

- Clinical observations (daily)
- Body weight (Days 0 and 7)
- Ophthalmoscopic Examinations
  - Direct ophthalmoscopic examination with fluorescein staining (prior to treatment and prior to necropsy)
  - Indirect ophthalmoscopic examination (prior to treatment)
  - Ocular examination according to Draize scale (twice daily)
- Gross pathology (after 7 days of treatment)
- Histopathology (globe of the eyes and adjacent tissues including upper and lower eyelids, nictitating membrane, lacrymal gland and optic nerve)

## RESULTS

### **Clinical Observations:**

No remarkable observations were noted.

### **Body Weight:**

No remarkable observations were noted.

### **Ophthalmoscopic Examinations:**

No remarkable observations were noted.

### **Gross Pathology:**

No remarkable observations were noted.

### **Histopathology:**

No remarkable observations were noted.

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**Key Study Observations:**

Under conditions of this study, 1, 2, and 4% w/v solutions of [redacted] 59002KP did not produce any adverse ocular effects in the pigmented eyes of Old English rabbits.

**STUDY IDENTIFICATION**

*SE 6190: Three-Month Toxicity Study in Old English Rabbits (v7 p 1)*

**Study Title:** Three-Month Toxicity Study in Old English Rabbits  
**Sponsor Study No.:** SE 6190  
**Study Dates:** May – August 1985  
**Report Date:** October 28, 1985  
**Test Facility:** [redacted]

**GLP Status:** Compliant with FDA GLPs

**METHODS**

**Test Article:** [redacted] 59002KP (Nedocromil sodium) 2% and 4% w/v  
**Batch No:** 2% Nedocromil sodium – P2288; 4% Nedocromil sodium – P2294  
**Purity:** Not stated  
**Vehicle Control:** Base formulation without Nedocromil sodium  
**Species/Strain:** Old English Rabbit (a strain with pigmented eyes)  
**No. of Animals/group:** 6 females  
**Route:** Topical ophthalmic  
**Dose Volume :** 1 drop/treatment  
**Concentration:** 0, 2, and 4% for Groups 1, 2, and 3, respectively  
**Treatment Schedule:** 1 drop 4 x per day Monday – Friday, and 1 drop 2 x per day Saturday and Sunday  
**Observations:** The following parameters were evaluated:

- Mortality (daily)
- Clinical observations (daily)
- Body weight (weekly)
- Food and Water Consumption (daily by visual examination)
- Ophthalmoscopic Examinations
  - Direct ophthalmoscopic examination
    - without fluorescein staining (twice daily)
    - with fluorescein staining (weekly)
  - Indirect ophthalmoscopic examination (prior to treatment and after 97 days of treatment)

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- Photography (prior to treatment and after 95 days of treatment)
- Ocular examination according to Draize scale (twice daily)
- Gross pathology (after 97 days of treatment)
- Histopathology (globe of the eyes and adjacent tissues including upper and lower eyelids, nictitating membrane, lachrymal gland and optic nerve)

## RESULTS

### **Mortality:**

One animal from the 4% Nedocromil sodium group was found dead prior to dosing on Day 21. Another animal was found dead prior to the initiation of treatment. Both animals had loose feces prior to death. Death of the treated animal is not attributable to treatment with Nedocromil sodium.

### **Clinical Observations:**

No remarkable observations were noted.

### **Body Weight:**

No remarkable observations were noted.

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### **Food and Water Consumption:**

No remarkable observations were noted.

### **Ophthalmoscopic Examinations:**

No remarkable observations were noted.

### **Gross Pathology:**

No remarkable observations were noted.

### **Histopathology:**

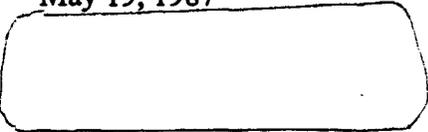
No remarkable observations were noted.

**Key Study Observations:**

Under conditions of this study, 2 and 4% w/v solutions of Nedocromil sodium did not produce any adverse ocular effects in the pigmented eyes of Old English rabbits.

**STUDY IDENTIFICATION**

*SE 6504: A 26-Week Ocular Toxicity Study of Nedocromil Sodium in the Rabbit (v7 p55)*

**Study Title:** A 26-Week Ocular Toxicity Study of Nedocromil Sodium in the Rabbit  
**Sponsor Study No.:** SE 6504  
**Study Dates:** March - October 1986  
**Report Date:** May 19, 1987  
**Test Facility:**   
**GLP Status:** Compliant with FDA GLPs

**METHODS**

**Test Article:** Nedocromil sodium (1%, 2% and 4%)  
**Batch No:** 1% Nedocromil sodium – P2473; 2% Nedocromil sodium – P2474; 4% Nedocromil sodium – P2475  
**Purity:** Not stated  
**Vehicle Control:** Colorless liquid supplied by the Sponsor  
**Species/Strain:** New Zealand White Rabbit  
**No. of Animals/sex/group:** 8  
**Route:** Topical ophthalmic  
**Dose Volume :** 0.04 ml  
**Concentration:** 0, 1, 2, and 4% for Groups 1, 2, 3 and 4, respectively  
**Treatment Schedule:** Four times daily (at approximate 2 hour intervals) for 6 months  
**Observations:** The following parameters were evaluated:

- Mortality (Daily)
- Clinical observations (Twice daily)
- Body weight (Weekly)
- Food consumption (Daily by visual examination)
- Ophthalmoscopic Examinations
  - Visual examination according to Draize (Daily)
  - Assessment of corneal color by visual examination (Weekly)
  - Ophthalmoscopic Examination including direct and

indirect examinations, tonometry, and pachymetry (prior to treatment and during weeks 2, 6, 15, and 25)

- Photography (Week 26)
- Clinical Pathology (prior to treatment and during weeks 14 and 26)
  - Hematology (hematocrit, red blood cell, platelet count, hemoglobin, white blood cell count, prothrombin time, Wintrobe's constants [calculated])
  - Clinical Chemistry (blood urea nitrogen, total protein, albumin, globulin (and A/G ratio), alkaline phosphatase, glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, total bilirubin, lactate dehydrogenase, glucose, sodium, potassium, chloride, calcium, cholesterol, creatinine)
- Gross pathology (study termination)
- Organ weights (adrenals, heart, kidneys, lungs, liver)
- Histopathology (eyes, eyelids, eye muscle, lachrymal ducts, nasal epithelium, optic nerve, liver, kidney, brain, heart, lungs)

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## RESULTS

### **Mortality:**

Deaths occurred in 1/16, 1/16, 2/16 and 0/16 animals in Groups 1, 2, 3 and 4, respectively. The deaths were attributed to anorexia, common to rabbits of this age and strain, and are not considered related to treatment.

### **Clinical Observations:**

No remarkable observations were noted.

### **Body Weight:**

No remarkable observations were noted.

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### **Food Consumption:**

Loss of appetite was occasionally noted in animals from all dose groups, and was the cause of death in animals that did not survive to termination. This finding is not unusual for this species and strain and is often accompanied by the presence of hairballs.

### **Ophthalmoscopic Examinations:**

Slight changes in the color of the cornea were noted after 3 weeks of treatment for all animals treated with 2% Nedocromil sodium and above, after 7 weeks of treatment for

animals treated with 1% Nedocromil sodium, and after 8 weeks of treatment with the vehicle control. The change was described as a "slight colorless shadow" that turned "yellowish" at Week 8 for animals treated with 2% Nedocromil sodium and above and at Week 13 for animals treated with 1% Nedocromil sodium. The changes persisted throughout the study for the 2 and 4% Nedocromil sodium groups and fluctuated between "colorless shadow" and "yellowish" for the 1% Nedocromil sodium group.

There were no remarkable observations recorded during visual examination of the eyes and scoring according to Draize.

There were no remarkable observation noted during direct and indirect ophthalmoscopy.

There were no abnormal findings in intraocular pressure measured by tonometry.

There were no remarkable observations noted in pachymetry examinations.

**Hematology:**

No remarkable observations were noted.

**Clinical Chemistry:**

No remarkable observations were noted.

**Gross Pathology:**

No remarkable observations were noted during gross observations or measurement of organ weights.

**Histopathology:**

No remarkable observations were noted.

**Key Study Observations:**

The only remarkable observation in this study was the slight discoloration of the cornea noted in animals treated with Nedocromil sodium. This "colorless shadow" or "yellowish" color was first noted during the second month of study and persisted throughout.

A follow-up study was conducted to further elucidate this finding, using a more rigorous and systematic evaluation of color changes, and the finding was not confirmed (SE 8686). The follow-up study is summarized below.

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**STUDY IDENTIFICATION**

*SE 8686: 6-month Ocular Investigative Study in the Male Rabbit (v6 p261)*

**Study Title:** 2% TILAVIST (an inhalation formulation of Nedocromil sodium) & 4% Nedocromil Sodium Ophthalmic Solution: 6-month Ocular Investigative Study in the Male Rabbit  
**Sponsor Study No.:** SE 8686  
**Study Dates:** February – September, 1993  
**Report Date:** November 30, 1990  
**Test Facility:**



**GLP Status:** Compliant with OECD Good Laboratory Compliance (1989)

**METHODS**

**Test Article:** Nedocromil sodium (2% and 4%)  
**Batch No:** 2% - P4038A; 4% - P4027A  
**Purity:** Not stated  
**Vehicle Control:** Aqueous solution containing benzalkonium chloride and disodium edetate  
**Species/Strain:** New Zealand White Rabbit  
**No. of Animals/group:**

Male New Zealand white rabbits were assigned to these treatment groups:

	Group 1	Group 2	Group 3
	Vehicle	2% Nedocromil	4% Nedocromil
	4 x 1 drop	4 x 1 drop	4 x 1 drop
Approximate* dose (mg/kg/day)	0	0.89	1.78
No. of main study animals	10	10	11†
No. of PK satellite animals	2	10	11†

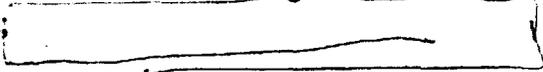
\* Using average 3.6 kg body weight at end of study.

† Additional animal added due to mortality on days 11 and 13

**Route:** Topical ophthalmic  
**Dose Volume :** One drop  
**Concentration:** 1, 2, and 4% for Groups 1, 2, and 3, respectively  
**Treatment Schedule:** Four times daily (at approximate 2 hour intervals) for 6 months  
**Observations:** The following parameters were evaluated:

- Mortality (Daily)
- Clinical observations (Twice daily)

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- Body weight (Weekly)
- Food consumption (Daily by visual examination)
- Water consumption (Daily by visual examination)
- Ophthalmoscopic Examinations
  - Direct and indirect ophthalmoscopic examination (Prior to treatment and after 1, 3 and 6 months of treatment)
  - Assessment of corneal color
    - Visual examination (Weekly)
    - Video image analyses (Prior to treatment and after 1, 3 and 6 months of treatment)
    - Photography (Prior to treatment and after 1, 3 and 6 months of treatment)
- Plasma concentration of Nedocromil sodium (Day 182 immediately after the fourth dose, and 5, 15, 30, and 90 minutes later; and on Day 183 prior to necropsy)
- Quantity of Nedocromil sodium in the Cornea (Samples collected from satellite animals after a single dose and after 3 months of treatment; 

## RESULTS

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### **Mortality:**

Deaths occurred in 0/12, 2/20, and 3/22 animals in Groups 1, 2, and 3, respectively. The deaths were attributed to loose feces, common to rabbits of this age and strain, and are not considered related to treatment.

### **Clinical Observations:**

Damp fur was noted around the eyes of treated and control animals. In some animals in treated with 4% Nedocromil sodium, the fur around the treated eye was observed to have transient yellow staining which resolved by the next dosing session (i.e., within approximately 2 hours).

### **Body Weight:**

No remarkable observations were noted.

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### **Ophthalmoscopic Examinations:**

No remarkable observations were noted upon direct and indirect ophthalmoscopic examination. There was not apparent abnormal coloration of the cornea observed during the course of the study. The computer image analyses of video and photographic recordings revealed similar patterns in hue for treated and non-treated eyes.

**Plasma Concentration of Nedocromil Sodium:**

Plasma concentrations peaked within 5 to 15 minutes post-dose and slowly declined over 90 minutes post dosing. Low plasma concentrations remained apparent approximately 18 hours after dosing. These data are summarized in the following table.

Plasma Concentration (ng/ml) of Nedocromil Sodium			
	Group 1 Vehicle 4 x 1 drop	Group 2 2% Nedocromil 4 x 1 drop	Group 3 4% Nedocromil 4 x 1 drop
$C_{max}$ Nedocromil sodium	<1	98 ± 13	201 ± 37
$C_{18\text{ hr}}$ Nedocromil sodium	<1	3.9 ± 0.9	7.3 ± 1.9

**Quantity of Nedocromil Sodium in the Cornea:**

Nedocromil sodium could not be measured in corneas from vehicle or low dose groups at any interval. Nedocromil sodium levels were slightly above the limit of detection (50 ng) in 2/5 and 1/5 animals receiving 4% Nedocromil sodium on Days 91 and 182, respectively.

**Key Study Observations:**

This study was conducted to elucidate the finding of yellow discoloration of the cornea reported in a previous study with the test material (SE 6504). The assessment of color change was not the subject of systematic study in the previous and the observation was believed to be the reflection of yellow-stained fur surrounding the eyes that resulted from the accumulation of the yellow-colored Nedocromil sodium; however, there was no mention of stained fur in the previous study. Eye color was systematically studied in this experiment and there was no evidence of yellow discoloration of the cornea. There were no other remarkable findings.

**Summary of Toxicology:**

In studies designed to assess local ocular irritation and systemic toxicity following ocular instillation of 4% Nedocromil sodium up to four times per day for up to six months, no evidence of ocular irritation, local toxicity, or systemic toxicity was noted. In addition, systemic toxicity was previously assessed under NDA 19-660, and Nedocromil sodium was found to be safe and has been described in approved product labeling for Tilade®.

**CARCINOGENICITY:**

Carcinogenicity studies were submitted and reviewed under NDA 19-660. The following is a summary of information that will be used to determine the labeling for the current NDA.

No increased tumor incidence was found in a 2-year inhalation carcinogenicity study in Wistar rats at doses of 8 or 24 mg/kg of metered dose inhaler (MDI) formulation (approximately 400 times the maximum recommended ophthalmic dose in adults on a mg/kg basis, based on a 50 kg adult). This was determined to be the maximum feasible inhalation dose. In the Carcinogenicity Assessment Committee (CAC) report dated October 17, 1991, the rat inhalation study was found to be valid and adequate.

No increased tumor incidence was found in a 2-year mouse dietary carcinogenicity study at a maximum dose of 180 mg/kg (approximately 3000 times the maximum recommended ophthalmic dose in adults on a mg/kg basis). However, the high dose was not near a maximum tolerated or maximum feasible dose for dietary intake. The dose was originally selected as a high multiple (approximately 500-fold) of the clinical MDI dose on a mg/kg basis. Systemic exposure in the mouse study was estimated to be approximately 20 times the human exposure for AUC of free drug based on PK data from a single-dose oral gavage study. However, a multiple-dose dietary PK study in mice (done as a phase 4 commitment in NDA 19-660) showed that the AUC after 5-weeks dietary administration at 180 mg/kg/day was lower than anticipated from the single-dose gavage data (review by M. Vogel, April 8, 1997). Based on an AUC of 57-ng·hr/mL and plasma protein binding of 30% in mouse, the AUC for free nedocromil is estimated at about 6 times the AUC in humans at the maximum recommended nebulizer dose. An exposure ratio of 6-fold is not, in itself, acceptable.<sup>11</sup> In addition, no human AUC value was provided following ophthalmic instillation of Nedocromil sodium; thus, AUC ratios cannot be used to justify the dose level.

In accordance with one of several options suggested by the Executive CAC (May 13, 1997), the Division may conclude that for the purposes of the clinical indication for which this product is used and the manner of its use, that the sum of the information available is adequate to indicate there is minimal risk of carcinogenic potential. This conclusion is justified and is applicable to this case, based on the observations that: 1) there was no indication of carcinogenic potential in the rat study or at the doses tested in mice; 2) because the drug is not metabolized in humans or animals there is no potential for activation to carcinogenic metabolites; 3) the approved inhalation dose (14 mg/day) is greater than the ophthalmic dose (3.2 mg/day); 4) no genotoxic effects have been identified in an appropriate battery of tests; and 5) no histopathological end organ toxicity has been identified. Taken together, the sum of information available suggests a minimal carcinogenic potential, and the drug was approved for inhalation use with a disclaimer in

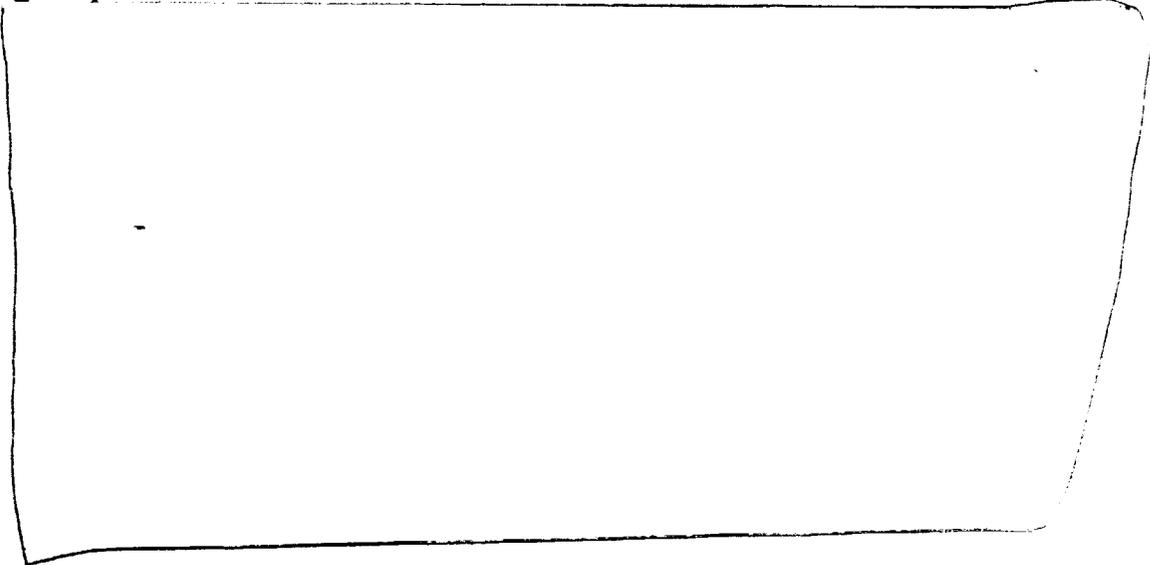
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<sup>11</sup> International Conference on Harmonisation; Guideline on Dose Selection for Carcinogenicity Studies of Pharmaceuticals, Federal Register, Vol. 60 No. 40, March 1, 1995.

the label indicating that carcinogenic potential may not have been fully explored in mice. It is recommended that this disclaimer be included in the labeling for Nedocromil Sodium 2% Ophthalmic Solution, as suggested in the "Recommendations to Sponsor" section of this review.

**REPRODUCTIVE TOXICOLOGY:**

Reproduction and teratology studies were reviewed under NDA 19-660 and the resultant labeling is reproduced as follows.



**GENETIC TOXICOLOGY:**

Genetic toxicology studies were reviewed under NDA 19-660 and the resultant labeling is reproduced as follows.



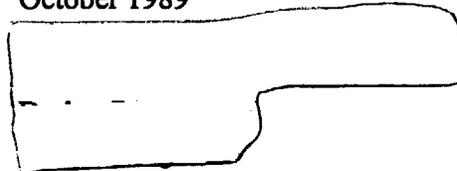
**SPECIAL TOXICOLOGY STUDIES:**

Nedocromil sodium was tested for ocular irritation in the presence of other ophthalmic products. The study is summarized below.

**STUDY IDENTIFICATION**

*SE 7197: Acute Ocular Irritation Interaction Study in the Rabbit with 2% Nedocromil Sodium Ophthalmic and Other Ophthalmic Products (v7 p380)*

**Study Title:** Acute Ocular Irritation Interaction Study in the Rabbit with 2% Nedocromil Sodium Ophthalmic and Other Ophthalmic Products  
**Sponsor Study No.:** SE 7197  
**Study Dates:** October 1988  
**Report Date:** October 1989  
**Test Facility:**



**GLP Status:** Compliant with OECD GLPs

**METHODS**

Test Article	Batch No.
2% Nedocromil sodium	P2867
Opticrom Eye Drops	X559
Ortivine Antistin Sterile Eye Drops	BN7134
Vasocon-A Eye Drops	JM1791
Betnesol-N	B6028DA
Predsol	B2498EA
Sno Phenicol 0.5%	BN804126
Timoptol 0.5%	82282
Sno Pilo 4%	BN803090

**Vehicle Control:** Saline (0.9%)  
**Species/Strain:** New Zealand White Rabbits  
**No. of Animals/group:** 3 males  
**Route:** Topical ophthalmic (one eye per animal)  
**Dose Volume (ml):** 0.05 ml Nedocromil sodium plus 0.05 ml of another ophthalmic product  
**Treatment Schedule:** One instillation every 2 hours for a total of four instillations  
**Observations:** The following parameters were evaluated:

- Ocular examination scored according to Draize (prior to each instillation and 24, 48, and 72 hours after the second application)

## RESULTS

### **Ocular Examinations:**

No remarkable observations were noted.

### **Key Study Observations:**

The 2% Nedocromil sodium solution, instilled with a variety of ophthalmic products, was non-irritating to the rabbit eye under conditions of this study.

## **OVERALL SUMMARY AND EVALUATION:**

The preclinical pharmacodynamic, pharmacokinetic, and toxicologic properties of Nedocromil sodium have been extensively studied and documented in NDA 19-660 for the metered dose inhaler formulation of nedocromil. A copy of the original Pharmacology/Toxicology review of NDA 19-660 is attached to this review. The following summary and evaluation focuses on the studies submitted in support of the ophthalmic use of Nedocromil sodium.

### Safety Evaluation:

No new safety issues were revealed in preclinical studies of Nedocromil sodium for ophthalmic use. Some suggestions for clear and accurate representation of data in the label are presented in the Labeling Review section that follows.

Nedocromil sodium inhibits a variety of inflammatory processes that may contribute to allergic conjunctivitis. It has been shown to prevent the release of several mediators of inflammation (e.g., histamine, IgE, prostaglandins, and leukotrienes) from a variety of cell types (e.g., mast cells, neutrophils, and eosinophils). Inhibition of both active and passive sensitization has been demonstrated in *in vivo* studies in rats and guinea pigs. *In vitro* studies are consistent with these findings.

Previous studies have shown that Nedocromil sodium is poorly absorbed from the gastrointestinal tract, with 0.2 to 11% oral bioavailability in mouse, 1 to 8% in rat, and 28% in dog. After intravenous administration, tissue distribution of Nedocromil sodium is mainly in the blood, kidney, liver and intestinal tract. Studies previously reviewed in NDA 19-660 show that Nedocromil sodium, when administered intravenously to pregnant rats is distributed at low levels in the fetal liver and yolk sac and is excreted in milk when administered intravenously to lactating rats. Low levels of Nedocromil sodium were detected in rat milk up to 48 hours after dosing. Plasma protein binding of Nedocromil sodium varies widely among species, at a concentration of 1 µg/ml binding

averaged 34% for mouse, 69% for rat, 72% for rabbit, 50% for dog and 82% for human. Nedocromil sodium is excreted unchanged and no metabolites have been identified in mouse, rat, rabbit, or dog. Nedocromil is rapidly eliminated from plasma with clearance rates of >300 ml/min/kg in mouse, approximately 70 ml/min/kg in rat, approximately 20 ml/min/kg in rabbit, and approximately 30 ml/min/kg in dog. The major route of excretion varies among species with a ratio of urinary:biliary percent excretion of 30:70 in mouse, 45:55 in rat, 95:5 in rabbit, and 60:40 in dog. The species with higher proportion of biliary excretion (mouse and rat) have more rapid clearance than the species with higher proportion of urinary excretion (rabbit and dog).

Studies submitted to the current NDA evaluated distribution and excretion of Nedocromil sodium after ocular instillation. These studies showed that Nedocromil sodium is rapidly cleared from the eye and is eliminated via feces (approximately 86%) and urine (approximately 6%) within 72 hours of dosing in the rat. Nedocromil sodium plasma levels reached a peak at 15 minutes (81.51 ng/ml) and declined to non-detectable levels by 6 hours in the rat after ocular instillation of 0.4 mg/kg. Nedocromil sodium was excreted unchanged in the feces and urine of rats, with a total recovery of 94.11% of the radioactive dose within 72 hours. Autoradiography in the rat revealed radioactivity in the eye immediately after dosing, which subsided to a very low level by 1 hour post dose and was not present in the eye at 24 hours. A very low level of radioactivity persisted in the large intestine until the 72-hour post dose observation.

No target organs of toxicity have been reproducibly identified for Nedocromil sodium. Previous studies indicate Nedocromil sodium has a relatively low order of toxicity. Studies specific to ophthalmic use include two acute studies in albino rabbits, 7-day and 3 month studies in pigmented rabbits, and two 6-month studies in albino rabbits. There were no signs of ophthalmic irritation or toxicity or systemic toxicity when rabbits were dosed up to 4 times per day with 4% Nedocromil sodium for up to 6 months. No signs of ocular irritation or toxicity were observed in an additional study, in which Nedocromil sodium was simultaneously instilled into the eyes of rabbits with each of nine different ophthalmic products.

#### Clinical Relevance of Safety Issues:

There are no new safety concerns for the use of Nedocromil sodium as an ophthalmic product. Previous preclinical studies submitted to support NDA 19-660 (Tilade®) and studies submitted to support the ophthalmic use of Nedocromil sodium support the safe use of Nedocromil sodium to treat allergic conjunctivitis as described in the submission.

#### Conclusions:

Previous studies submitted and reviewed under NDA 19-660 and supporting INDs along with new studies relevant to ophthalmic use of Nedocromil sodium support the clinical use of this drug to treat allergic conjunctivitis as described in the submission.

**LABELING REVIEW:**

Carcinogenicity studies submitted to NDA 19-660 were the subject of a full Carcinogenicity Assessment Committee (CAC) review on June 27, 1990. The rat study was found acceptable but the mouse study failed to achieve doses high enough to adequately test carcinogenic potential in this species. The Sponsor subsequently conducted additional pharmacokinetic studies to see whether exposure levels could provide sufficient justification for the selection of the high dose; which they did not. Labeling indicating that doses used in the mouse study may not have been high enough to fully evaluate the carcinogenic potential in this species, was recommended by the Executive CAC.

This statement, as well as other modifications, should be incorporated into the label as suggested in the "Recommendations to Sponsor" section that follows.

**RECOMMENDATIONS TO SPONSOR:**

Specific suggestions to preclinical sections of the proposed labeling are recommended and should be conveyed to the Sponsor as they are written below.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The labeling should be modified to read as follows:

**DRAFT  
LABELING**

Pregnancy

The labeling should be modified to read as follows:

**DRAFT  
LABELING**

Overdosage

Information on overdosage should added to the label as follows.

**DRAFT  
LABELING**

THIS WAY  
ORIGINAL

**REVIEWER SIGNATURE/TEAM LEADER SIGNATURE:**

*[Signature]*  
8/24/99

Tracey Zoehs, M.S.  
Pharmacology/Toxicology Reviewer

*[Signature]*  
2/11/99

Andrea Weir, Ph.D.  
Pharmacology/Toxicology Team Leader

- cc: NDA 21-009  
HFD-550/Division Files  
HFD-550/PM/Gorski  
HFD-550/PT/Zoetis  
HFD-550/MO/Dunbar  
HFD-550/Dep. Dir./Chambers  
HFD-550/Biopharm/Tandon  
HFD-550/Chem/Tso  
HFD-550/Stat/Li

APPROVED THIS WAY  
ON 08/24/99