

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20750

CHEMISTRY REVIEW(S)

600.1051

FEB 24 1997

Division of Pulmonary Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-750 CHEM. REVIEW #: 1 REVIEW DATE: February 21, 1997

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
Original 30-SEP-96 01-OCT-96 16-OCT-96

NAME AND ADDRESS OF APPLICANT:

500 Arcola Road
Collegeville, PA 19426

ATTN: Dr. Steven J. Miller
Associate Director
Regulatory Affairs
Tel: (610) 454-3221

DRUG PRODUCT NAME:

Proprietary: Tilade® Nebulizer Solution
Nonproprietary/USAN: Nedocromil sodium inhalation solution
Code Name/#:
Chem. Type/Ther. Class: 3
Established Name of Drug Substance: Disodium 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4H-pyrano[3,2-g]quinoline-2,8-dicarboxylate

PHARMACOL. CATEGORY/INDICATION:

Maintenance therapy in the management of patients with mild to moderate asthma

DOSAGE FORM:

Nebulizer solution

STRENGTHS:

The solution contains nedocromil sodium with w/v sodium chloride to adjust the tonicity and hydrochloric acid as needed to adjust the pH to 4.85 (4.0 to 5.5). The solution is provided in LDPE ampules, each containing 2.2 mL.

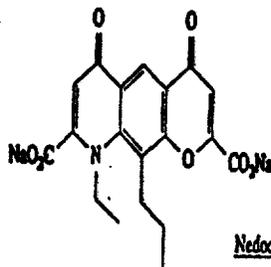
ROUTE OF ADMINISTRATION:

Oral Inhalation

Rx/OTC:

Prescription

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:



Nedocromil Sodium

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NDA 20-750
Tilade® Nebulizer Solution
page, 2

SUPPORTING DOCUMENTS:

CONSULTS:

1. Since Tilade is an already approved name, a trademark consult is not necessary.
2. An EER request was submitted on 11/22/96 for all facilities involved in synthesis, release and stability testing of drug substance and manufacturing, packaging, in-process testing, release and stability testing of drug products.
3. Biometrics consult for the proposed expiration dating period will be requested shortly. The applicant has provided 12 months' stability data. They are requesting 24 months expiration dating period.
4. EA will be reviewed separately once we receive information on the Expected Introduction Concentration (EIC)

NDA 20-750
Tilade[®] Nebulizer Solution
page, 3

REMARKS/COMMENTS:

1. Methods validation by the Agency should be deferred pending resolution of deficiencies in the methods as requested.
2. The drug product is photolabile; all labels including overwrap should state that the product to be kept "protected from light".

CONCLUSION AND RECOMMENDATION:

This NDA should be considered to be not approvable from CMC standpoint.

Chong-Ho Kim 2/24/97
Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc:
Orig. NDA #20-750
HFD-570 Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/MVogel
HFD-570/BGallauresi
R/D Init. by: *GR 2/24/97*
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AUG 6 1997

Division of Pulmonary Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-750 CHEM. REVIEW #: 2 REVIEW DATE: August 06, 1997

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	30-SEP-96	01-OCT-96	16-OCT-96
Amendment [BZ]*	12-MAY-97	13-MAY-97	15-MAY-97
Amendment [BC]*	25-JUN-97	26-JUN-97	30-JUN-97

*Subject of this review

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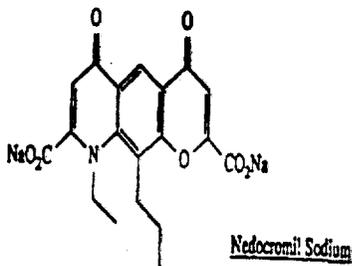
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Rx/OTC:

Prescription

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:



BEST POSSIBLE COPY

NDA 20-750
Tilade[®] Nebulizer Solution
page 2

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CONSULTS:

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2. An EER request was submitted on 11/22/96 for all facilities involved in synthesis, release and stability testing of drug substance and manufacturing, packaging, in-process testing, release and stability testing of drug products. All facilities have been inspected and found acceptable (July 23, 1997).
3. Biometrics consult was not requested for the following reasons:
 - Applicant has requested 24 months expiration dating period(25°C/AMBH) and actual data for 24 months are provided.

NDA 20-750

Tilade® Nebulizer Solution

page 3

- Evaluation of the stability data suggests no particular trends in pH, assay, and impurities; pH drops in three months and remains pretty steady for 24 months. Impurities are barely quantifiable until 18 months and picks up a little bit at 24 months.

REMARKS/COMMENTS:

1. Methods validation by the Agency should be deferred pending resolution of deficiencies in the methods as requested.
2. The drug product is photolabile; all labels including overwrap should state that the product to be kept "protected from light".

CONCLUSION AND RECOMMENDATION:

The NDA is not approvable from CMC standpoints.

Chong-Ho Kim 8/6/97
Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc:

Orig. NDA #20-750
HFD-570 Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/Totulana
HFD-570/MVogel
HFD-570/BGallauresi
R/D Init. by: *CS 8/6/97*

doc.NDA 20-750.CR2

SEP 23 1997

Division of Pulmonary Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-750

CHEM. REVIEW #: 3 REVIEW DATE: September 22, 1997

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	30-SEP-96	01-OCT-96	16-OCT-96
Amendment [BZ]	12-MAY-97	13-MAY-97	15-MAY-97
Amendment [BC]	25-JUN-97	26-JUN-97	30-JUN-97
Amendment [BC] *	04-SEP-97	05-SEP-97	05-SEP-97
Amendment [BL] *	17-SEP-97	18-SEP-97	18-SEP-97
Amendment [BC] *	18-SEP-97	19-SEP-97	19-SEP-97

*Subject of this review

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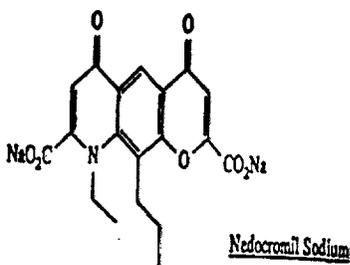
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NDA 20-750
Tilade[®] Nebulizer Solution
page 2

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2. An EER request was submitted on 11/22/96 for all facilities involved in synthesis, release and stability testing of drug substance and manufacturing, packaging, in-process testing, release and stability testing of drug products. All facilities have been inspected and found acceptable (July 23, 1997).
3. Biometrics consult was not requested for the following reasons:
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NDA 20-750

Tilade^o Nebulizer Solution

page 3

- Evaluation of the stability data suggests no particular trends in pH, assay, and impurities; pH drops in three months and remains pretty steady for 24 months. Impurities are barely quantifiable until 18 months and picks up a little bit at 24 months.
4. Microbiology review dated June 13, 1997 recommends approval for the NDA on the basis of sterility assurance. However, the applicant should be

REMARKS/COMMENTS:

1. Amendment dated September 19, 1997 contains modified versions of "Tests and Specifications" and "Stability Protocol" for Tilade Nebulizer Solution. The amendment is acceptable.
2. Methods validation for the regulatory methods will be requested shortly.
3. Applicant commits to set a specification for
4. The drug product is photolabile; all labels including overwrap should state that the product to be kept "protected from light".
5. From CMC viewpoint the package insert dated September 17, 1997 is adequate. However, labels are missing.

CONCLUSION AND RECOMMENDATION:

The NDA is approvable from CMC standpoints. The applicant should be reminded of their commitment to submit

The applicant needs to submit final markup labels for evaluation prior to approval.

Chong-Ho Kim 9/22/97
Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc:

Orig. NDA #20-750
HFD-570 Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/Totulana
HFD-570/MVogel
HFD-570/BGallauresi
R/D Init. by: *OK* 9/22/97

doc.NDA 20-750.CR3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20750

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-750

**TILADE Nebulizer Solution
(Nedocromil Sodium Inhalation Solution)**

Division of Pulmonary Drug Products, HFD-570

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-750

TILADE Nebulizer Solution
(Nedocromil Sodium Inhalation Solution)

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (Section 101), and provides procedures (Section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment. FDA actions are to be supported by accurate scientific analyses. Also, environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research, in accordance with E.O. 12114, 21 CFR 25.50, and 21 CFR 25.22(a) has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared. The Division of Pulmonary Drug Products has reviewed the environmental assessment and has determined that approval NDA 20-750 (TILADE Nebulizer Solution) will have no significant environmental impact.

In support of their new drug application, Rhone-Poulenc Rorer has prepared an environmental assessment in accordance with 21 CFR 25.31a(a) which evaluates the potential environmental impacts of the manufacture, use, and disposal of TILADE Nebulizer Solution attached. Approval of this NDA for Tilade Nebulizer Solution will make this treatment available for use, in the United States, in the clinically demonstrated inhibition of bronchoconstriction and brochial hyperresponsiveness in asthmatic patients.

The environmental assessment and FONSI are applicable to the New Drug Application (NDA) for this product. The firm's environmental assessment includes an on-site evaluation (the quantities and concentrations estimated to the extent possible) of the substances emitted into the environment and information on applicable environmental permits and regulations.

The Maximum Expected Emission Concentration of Nedocromil Sodium due to use of Rhone-Poulenc Rorer drug products is less than one part per billion, the concentrations of drug substances for human use that CDER has routinely found to have no significant effect on relevant standard test organisms, and are therefore unlikely to have a significant effect on the environment.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the drug product is expected to minimize occupational exposures and environmental emissions.

7/2/97
DATE

Chong-Ho Kim
PREPARED by
Chong-Ho Kim, Ph.D.
Review Chemist
Division of Pulmonary Drug Products
Center for Drug Evaluation and
Research

7/3/97
DATE

Guirag Poochikian
DIVISION CONCURRENCE
Guirag Poochikian, Ph.D.
Chemistry Team Leader, DNDC II
Division of Pulmonary Drug Products
(HFD-570)
Office of Drug Evaluation II
Center for Drug Evaluation and
Research

7/11/97
DATE

Nancy B. Sager
CONCURRED
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and
Research

Attachment: Releasable Environmental Assessment
 Material Safety Data Sheet (drug substance)

6

*****SENSITIVE*****

**REVIEW
OF
ENVIRONMENTAL ASSESSMENT
FOR
NDA 20-750
TILADE[®] Nebulizer Solution
(Nedocromil Sodium Inhalation Solution)**

**Division of Pulmonary Drug Products, HFD-570
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE COMPLETED: 5-12-97

2) Fisons plc
London Road
Holmes Chapel
Crewe
Cheshire CW4 8BE
England

ii. **Drug Product:**
The Tilade Nebulizer Solution will be manufactured, packaged and labeled at:

Automatic Liquid Packaging, Inc.
Packaging Division
2200 W. Lake Shore Drive
Woodstock, Illinois 60098

d. **Locations of Use**
Throughout the United States.

e. **Disposal Sites**

Returned Tilade Nebulizer Solution will be sent from the Rhone-Poulenc Rorer Distribution Centers for disposal via incineration at the permitted incineration facility of Savannah Energy Systems company.

Comments: Locations for production, use and disposal are adequately described.

Item 5. IDENTIFICATION OF CHEMICAL SUBSTANCES.

Chemical name, formula, molecular weight, physical description, CAS number and structural formula of the drug substance are provided. Excipients and impurities are also briefly described.

Evaluation: Satisfactory.

Item 6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT.

a. **Substances expected to be emitted**

The drug substance is prepared by two methods. A certification of compliance with environmental regulations for the Jurong, Singapore facility is provided (Attachment I) and for Cheshire, England facility

(Attachment II).

b. Controls exercised

Rejected nedocromil sodium drug substance at the Automatic Liquid Packaging site will be returned to the drug substance manufacturer for recovery or disposable as appropriate, or sent for disposal via the permitted waste hauler.

Comments: There is no discussion of controls used for air and liquid emissions at the Automatic Liquid Packaging Site (e.g., filters, pretreatment of liquid waste prior to discharge to POTW).

Deficiency: Please provide discussion of controls used for air and liquid emissions at the Automatic Liquid Packaging Site (e.g., filters, pretreatment of liquid waste prior to discharge to POTW).

c. Citation of and Statement of Compliance with Applicable Emission Requirements

The process does not include any chemical modification or treatment of drug substance nedocromil sodium and does not involve the use of organic solvents.

A certification of compliance for the Automatic Liquid Packaging facility is provided (Attachment III). MSDS for nedocromil sodium also is provided(Attachment IV). However, it should be classified as nonconfidential appendix.

Comments: A citation of all applicable Federal, State and local emission requirements, including occupational should be provided. Emission permits and licenses should have the number, authorization agency and expiration dates.

Deficiencies:

Please provide a citation of all applicable. Federal, State and local emission requirements, including occupational. Emission permits and licenses should have the number, authorization agency and expiration dates.

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

The incremental change at the drug substance manufacturing sites as a

result of approval of this NDA will not have a significant impact. (See EIC data) - Satisfactory.

e. **Expected Introduction Concentrations**

Calculation of the Expected Introduction Concentration (EIC) for all formulations of nedocromil sodium is still below 1 ppb. Therefore, Tier 0 approach is taken.

NOTE: In using the Tiered approach to fate and effects testing proposed by the Agency, the Environmental Assessment format items 7,8,9,10 and 11 need not be addressed since the EIC for nedocromil sodium meets the requirement for Tier 0 (<1 ppb).

Item 12. LIST OF PREPARERS

Dr. William Studt
Process chemistry & Biochemistry
Regulatory Documentation
Rhone-Poulenc Rorer
Collegeville, PA

Item 13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of Rhone-Poulenc Rorer.

Comment: Satisfactory.

Item 14. REFERENCES

No references are provided.

Item 15. Appendices:

Following attachments are provided:

Attachment I:	Certification of Compliance- Singapore
Attachment II:	Certification of Compliance- Cheshire, UK
Attachment III:	Certificate of Compliance- Automatic Liquid Packaging
Attachment IV:	MSDS for Nedocromil Sodium
Attachment V:	CV of Preparer
Attachment VI:	Certification

Comments: Satisfactory.

Deficiencies:

1. Please provide discussion of controls used for air and liquid emissions at the Automatic Liquid Packaging Site (e.g., filters, pretreatment of liquid waste prior to discharge to POTW). [Item 6.b.]
2. Please provide a citation of all applicable. Federal, State and local emission requirements, including occupational. Emission permits and licenses should have the number, authorization agency and expiration dates.[Item 6.c.]

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20750

PHARMACOLOGY REVIEW(S)

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
 Original Review

NDA No. 20-750

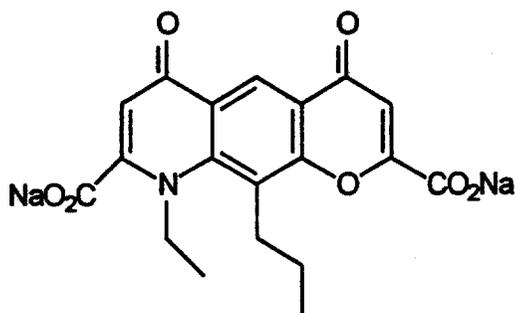
Submission Dates: 30 SEP 96, 11 FEB 97, 25 JUL 97

Reviewer: W. Mark Vogel, Ph.D.

Review Completed: 09 SEP 97

Information to be Conveyed to Sponsor: Yes (✓), No ()

Sponsor: Rhone-Poulenc Rorer, Collegeville, PA

Drug Names:*Proprietary Name:* Tilade® Nebulizer Solution*Established Name:* Nedocromil sodium inhalation solution*Code Names:* FPL 59002KP, FR 107265*Chemical Name:* 4H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid-9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-, disodium salt**Structure:**

Molecular Weight:415.31

Chemical Formula:.....C₁₉H₁₅NNa₂O₇

CAS No.:.....69049-74-7

Class:Anti-allergic

Indication: Mild to moderate asthma in patients aged 2 and older**Route of Administration:** Inhalation

Clinical Formulation: Solution for nebulization. Each low density polyethylene ampule contains 11 mg nedocromil sodium in 2.2 mL of aqueous solution made isotonic with sodium chloride; hydrochloric acid is used to adjust the pH within the range 4.0 to 5.5.

Dosage: One ampule (11 mg) 4 times daily (44 mg); maximum recommended dose is 3.67 mg/kg/day in a 12 kg 2-year-old (84 mg/m²), 0.88 mg/kg/day in a 50 kg adult (33 mg/m²).

Related INDs/NDAs/DMFs:

Preclinical Studies Submitted and Reviewed in this NDA: No preclinical studies were done specifically to support the nebulizer inhalation solution. The sponsor claims that the extensive preclinical data submitted to support the approved nedocromil MDI (NDA 19-660) support the nebulizer solution. The Pharm/Tox review of NDA 19-660, 29 MAY 1987, by Clyde Oberlander is attached. In the present application (NDA 20-750) the sponsor references several pharmacokinetic and toxicology studies submitted to IND 21,544 after approval of NDA 19-660 as additional support for the present application. Those studies are cited either because they used improved analytical methods with lower limits of detection for nedocromil or because they used increased systemic exposures compared to previous studies. Many pharmacology studies were submitted to IND 21,544 after approval of NDA 19-660. Only those pharmacology studies that support new preclinical claims in the proposed labeling are reviewed here.

Preclinical Studies Reviewed for this NDA:

Study	Study Number	Submitted to	Date Submitted
Pharmacology Studies			
Neurogenic inflammation in rat airways	SD11898		11/18/92
Citric acid induced cough in guinea pigs	R78D/3		11/30/93
Cough and bronchoconstriction in guinea pigs	T08B		03/24/94
NANC contraction of guinea pig bronchi	(Am Rev Respir Dis 143:114, 91)		
Effect on isolated rabbit vagus nerve	(Eur J Pharmacol 221:175, 92)		
Substance P & cholinergic responses, rabbit trachea	(J Auton Pharmacol 11:167, 91)		
Sensory nerve mediated contraction of rabbit iris	FSS3		08/01/95
Metabisulfite bronchoconstriction, allergic sheep	R33D/2		07/21/93
PAF-induced airway responses in allergic sheep	(J Allergy Immunol 85:661, 90)		
Absorption, Distribution, Metabolism and Excretion Studies			
Rat single dose dry powder inhalation PK	SE 7552		07/21/93
Rat single dose MDI inhalation PK	SE 7618		08/01/95
Rat fetal transfer study	SE 8993		08/01/95
Elimination of radiolabel in milk (rat, i.v.)	SE 9147		03/24/94
Rat, dog, human serum protein binding	SE 9378		08/01/95
Hepatic P450 enzyme induction in rats (i.v.)	SE 9380		08/01/95
Acute Toxicity Studies			
Acute p.o. and i.v. toxicity in rats	SE 8384		06/11/92
Acute i.v. toxicity in adult dogs	SE 8385		07/23/92
Multiple Dose Toxicity Studies			
Rat 3-month subcutaneous toxicity	SE 9898		04/03/96
Rabbit 6-month ocular toxicity	SE 8686		08/01/95

Reproduction and Genotoxicity Studies

Rat segment II teratology dose-ranging (s.c.)	SE 9900	04/03/96
Rat segment II teratology study (s.c.)	SE 9901	04/03/96
Mouse micronucleus (higher dose)	SE 9873	04/03/96

Special Toxicity Studies (Impurities)

Acute i.v. toxicity of impurities in mouse	SE 8799	08/01/95
Acute ocular toxicity of impurities in rabbit	SE 8800	08/01/95
Rat 1-wk i.v. toxicity of impurities	SE 8883	08/01/95
Rat 1-month i.v. toxicity of FPL 67908KP	SE 8884	08/01/95
Rat 1-month i.v. toxicity of FPL 64359KA	SE 8908	08/01/95
Ames test for FPL 67908KP	SE 9053	08/01/95
Ames test for FPL 64359KA	SE 9089	08/01/95
CHO cytogenetics with FPL 67908KP	SE 8959	08/01/95
Human lymphocyte cytogenetics, FPL 64359KA	SE 9087	08/01/95

Studies Previously Reviewed:

Acute toxicity in 3-wk old dogs (i.v.) *	SE 9253	04/03/96
Rising-dose acute tolerance, 3-wk old dogs *	SE 9254	03/24/94
Mouse multiple dose dietary PK study †	SE 8399	NDA 19-660 12/22/93

*NDA 19-660, supplement SE6-015, reviewed by Y.S. Choi, 18 JUN 96

†NDA 19-660, reviewed by W.M. Vogel, 08 APR 97

Studies Not Reviewed in this NDA: N/A

Note: Portions of this review were excerpted directly from the sponsor's submission.

PHARMACOLOGY

Nine pharmacology studies support two new proposed preclinical labeling claims:

a) "Nedocromil sodium inhibits neuronally mediated responses in a variety of *in vitro* and *in vivo* tests" b) "Nedocromil sodium also reduced PAF-induced airway responses when administered by inhalation with a nebulizer in another model system".

Neurogenic Inflammation in Rat Airways

Study SD 11898,

Methods: Pentobarbital anesthetized male rats were treated with the metallopeptidase inhibitor thiorphan (100 µg/kg, i.v.) to enhance tachykinin effects and with atropine (1 mg/kg, i.v.) to block cholinergic effects. ¹²⁵I-albumin in 2% Evans blue dye was administered intravenously as a marker for microvascular leakage. After these pre-treatments test drug was administered and 5 minutes later the cut cervical vagi were stimulated to elicit neurogenic inflammation. After 10 minutes tracheas were excised and extravasation of ¹²⁵I-albumin was determined by gamma counting.

Results: Nedocromil alone (30 mg/kg, i.v.) had no effect on vascular leakage. Salbutamol alone (3 µg/kg, i.v.) had only a minor effect on vascular leakage (25%↓); The combination of nedocromil and salbutamol at those doses caused a significantly greater reduction in vascular leakage (55%↓) than either treatment alone.

Citric Acid Induced Cough In Conscious Guinea Pigs.

Methods: Cough was induced in conscious male guinea pigs by exposure to a nebulized solution of 500 mM citric acid with and without pretreatment with nebulized saline or 2% nedocromil sodium for 5 minutes before cough challenge. The number of coughs were counted during 10 minutes continuous exposure.

Results: The number of citric acid induced coughs after nedocromil pretreatment (56 coughs/10 minutes) did not differ significantly from that observed after saline pretreatment (61 coughs/10 minutes).

Cough and Bronchoconstriction In Guinea Pigs.

Methods: Cough was induced in conscious female guinea pigs by 2 minute exposures to nebulized solutions of 100 mM and 300 mM citric acid (stimulates rapidly adapting receptors) and 10 or 30 µM capsaicin (stimulates c-fibers). Coughs were counted during the 2 minute challenge and the following 10 minutes. Either 10 or 30 µM capsaicin was used, whichever produced a cough frequency greater than 5/session for each animal. Animals were exposed to cough-stimulants on different days with 15 minutes nebulized saline or 2% nedocromil sodium pretreatment before challenge. In separate experiments, bronchoconstriction was induced in urethane anesthetized guinea pigs with aerosolized capsaicin (30 µM for 1 minute via tracheal cannula), or by i.v. infusions of substance-P (1 µg/min) or neurokinin A (0.1 µg/min). After a stable constriction was reached, aerosols of either 0.9% saline or 2% nedocromil sodium were administered for 1 minute. Airway resistance was calculated from measurements of airflow and pleural pressure.

Results: Nedocromil decreased the number of coughs per session from 20.5±3.4 to 13.5±2.8 for 300 mM citric acid (34%↓); nedocromil did not significantly reduce cough induced by 100 mM citric acid. Nedocromil decreased the number of coughs from 9.3±1.0 to 4.1±0.8 for capsaicin (56%↓). Capsaicin increased airway resistance from 6.3±0.9 to 15.5±2.1 mmHg/L/min (146%↑). Nedocromil decreased the airway resistance after capsaicin to 11.5±1.7 mmHg/L/min (43% inhibition of capsaicin effect), but had no effect on bronchoconstrictor responses to i.v. substance-P or neurokinin A. The investigators conclude that nedocromil inhibited cough and capsaicin induced bronchoconstriction, by an effect on airway sensory nerves.

Non-Adrenergic Non-Cholinergic (NANC) Contraction of Guinea Pig Bronchi

G.M. Verleden et al., National Heart and Lung Institute, UK, Am Rev Respir Dis 143:114, 91,
cited in NDA 20-750, submitted 9/30/96, volume 5, page 5-1-70.

Methods: Ring segments of bronchi or tracheal strips isolated from male guinea pigs were maintained in organ baths connected to force transducers. NANC mediated bronchoconstriction was elicited by electrical field stimulation in the presence of indomethacin plus atropine to block cholinergic responses. Various agonists were added to the bath to determine the effect on NANC responses.

Results: Nedocromil (10^{-8} to 10^{-4} M) caused dose related inhibition of NANC bronchoconstriction ($40 \pm 4\%$ inhibition at 10^{-4} M nedocromil). Cromolyn sodium (10^{-4} M) caused only a $9 \pm 8\%$ inhibition of NANC contraction. Nedocromil had no effect on contractile responses to substance-P (10^{-9} to 10^{-5} M) and did not alter the cholinergic response to field stimulation in isolated trachea. The investigators conclude that nedocromil modulates release of tachykinins from airway sensory nerves.

Effect on Isolated Rabbit Vagus Nerve

Jackson et al., Fisons Laboratories, UK, Eur J Pharmacol 221:175, 92,
cited in NDA 20-750, submitted 9/30/96, volume 5, page 5-1-72.

Methods: Cervical vagi were dissected from young adult white rabbits. The desheathed nerves were mounted in organ baths and potential changes were measured with Ag/AgCl electrodes. Various agonists were added to the bath and left in contact until a maximal response was achieved. The majority of the fibers in this nerve are sensory type C-fibers.

Results: Nedocromil sodium (3×10^{-6} to 10^{-3} M) caused a slow depolarization of the nerve, in contrast to a rapid response elicited by addition of serotonin. The depolarization was not maintained and once it had occurred could not be repeated for an hour. Removal of chloride from the Krebs solution or addition of the chloride channel blocker 4,4'-diisothiocyanostilbene-2,2'-disulphonic acid (10^{-5} M) abolished the depolarizing response to nedocromil. Cromolyn sodium, up to 10^{-3} M, did not depolarize the nerve. The investigators suggest that nedocromil depolarized the rabbit vagus by opening a chloride channel, after this opening it is possible that the channel is then blocked.

Substance-P and Cholinergic Responses in Innervated Rabbit Trachea

C.L. Armour et al., University of Sydney, J. Auton. Pharmacol. 11:167, 91,
submitted 11/18/92 to IND 21,54, serial N127

Methods: Force responses were measured in isolated rabbit trachea. Parasympathetic preganglionic stimulation was achieved by electrical stimulation of the attached vagus nerve; postganglionic stimulation was achieved by transmural electrical field stimulation. The effects of substance-P (10^{-6} M) on pre- and postganglionic responses were measured with or without nedocromil pretreatment (10^{-7} M).

Results: Substance-P potentiated contractions induced by parasympathetic stimulation at the preganglionic site ($207 \pm 38\% \uparrow$) and the postganglionic site ($207 \pm 61\% \uparrow$). Nedocromil sodium inhibited the effect of substance-P on preganglionic stimulation ($52\% \downarrow$ in substance-P effect) but not postganglionic stimulation. The investigators conclude that nedocromil sodium modifies neuropeptide action selectively at a preganglionic site.

Sensory Nerve Mediated Contraction of Rabbit Iris

Methods: Rabbit iris sphincter muscles were isolated, mounted in organ baths and stimulated to contract by electrical field stimulation. Atropine ($1 \mu\text{M}$) was added to the bath to block the early cholinergic component of the contractions.

Results: Nedocromil, at $10 \mu\text{M}$ but not at $1 \mu\text{M}$, significantly reduced contractions to electrical field stimulation or contractions elicited by addition of bradykinin ($1 \mu\text{M}$) to the bath. Responses to capsaicin or substance-P were not inhibited by nedocromil. In the rabbit iris, non-adrenergic, non-cholinergic (NANC) responses to electrical field stimulation and responses to bradykinin are believed to be due to release of tachykinins, such as substance P, from sensory nerve endings. These observations suggest that nedocromil may inhibit neuronal release of tachykinins from sensory nerve endings.

Metabisulfite Bronchoconstriction in Allergic Sheep

Methods: Bronchoconstrictor responses to increasing concentrations (25, 50, and 100 mg/mL) of nebulized sodium metabisulfite solution were measured in conscious restrained sheep with naturally occurring allergy to *Ascaris suum*. The provoking concentration causing a 100% increase of airway resistance (PC_{100}) was calculated by interpolation from the dose response curve. Metabisulfite dose response curves were generated with or without pretreatment with nedocromil sodium (1 mg/kg, inhalation), ipratropium bromide (180 μg , inhalation), or chlorpheniramine (2 mg/kg, i.v.).

Results: The baseline PC_{100} for metabisulfite was 39 ± 10 mg/mL. Pretreatment with ipratropium decreased the sensitivity to metabisulfite, increasing the PC_{100} to 92 ± 8 mg/mL. Nedocromil pretreatment also decreased the sensitivity to metabisulfite, increasing the PC_{100} to 100 ± 0 mg/mL. The H_1 antagonist chlorpheniramine had no significant effect on the sensitivity to metabisulfite, $\text{PC}_{100} = 45 \pm 10$ mg/mL.

PAF-Induced Airway Responses in Allergic Sheep
M. Soler et al., *J Allergy Immunol* 85:661, 90,
cited in NDA 20-750, submitted 9/30/96, volume 5, page 5-1-63.

Methods: Bronchoconstrictor responses to platelet activating factor (PAF) were measured in conscious restrained sheep with natural allergy to *Ascaris suum*. Animals were pretreated with aerosol saline or nedocromil (1 mg/kg), and airway resistance was measured after tracheal instillation of 30 $\mu\text{g}/\text{kg}$ PAF. To assess bronchial hyperreactivity, the provocative dose of carbachol, in breath units (BU) needed to increase resistance to 4 $\text{L}\cdot\text{cm H}_2\text{O}\cdot\text{s}^{-1}$ (PD4), was determined at 2 and 24 hours after PAF administration.

Results: Nedocromil inhibited the initial bronchoconstrictor response to PAF by 87%. In the absence of nedocromil, PAF increased bronchial responsiveness as indicated by a decrease in the carbachol PD4 from 39 ± 9 BU at baseline to 16 ± 8 BU at 2 hours after PAF and 26 ± 16 BU at 24 hours after PAF. With nedocromil pretreatment there was not a significant increase in the sensitivity to carbachol; PD4 was 35 ± 7 BU at 2 hours after PAF and 26 ± 16 BU at 24 hours after PAF.

Summary of Pharmacology

Studies cited in NDA 20-750 to support new preclinical labeling claims are summarized as follows:

- Nedocromil, 30 mg/kg i.v., in rats, had no effect alone but acted synergistically with the β -agonist, salbutamol, to inhibit tracheal vascular leakage after vagal stimulation.
- Nedocromil, 2% aerosol for 5 minutes, had no effect on cough induced by 10 minutes exposure to 500 mM citric acid in guinea pigs.
- Nedocromil, 2% for 15 minutes, inhibited cough induced by 2 minutes exposure to 300 mM citric acid or 10-30 μM capsaicin in guinea pigs. Nedocromil inhibited bronchoconstriction to inhaled capsaicin but not to i.v. substance-P or neurokinin A.
- Nedocromil (10^{-8} to 10^{-4} M) inhibited NANC mediated contraction of isolated guinea pig bronchi but not contractions mediated by addition of substance-P to the bath.
- In, isolated rabbit vagus, composed primarily of sensory type C-fibers, nedocromil (3×10^{-6} to 10^{-3} M) caused a depolarizing blockade mediated via chloride channels.
- Nedocromil (10^{-7} M) inhibited the ability of substance-P to potentiate contractions of isolated rabbit trachea elicited by preganglionic parasympathetic stimulation.
- Nedocromil (10 μM) inhibited contractions of isolated rabbit iris evoked by electrical field stimulation or bradykinin, but not those evoked by substance-P or capsaicin.
- Nedocromil (1 mg/kg, inhalation) decreased the sensitivity to metabisulfite induced bronchoconstriction in allergic sheep.

- In allergic sheep, nedocromil inhalation (1 mg/kg,) inhibited the immediate broncho-constrictor response to tracheal instillation of PAF and inhibited the development of bronchial hyperreactivity after exposure to PAF as measured by carbachol sensitivity.

PHARMACOKINETICS AND TOXICOKINETICS

Rat Single Dose Dry Powder Inhalation Pharmacokinetics Study SE 7552, Submitted 07/21/93 to IND

Methods: Wistar rats (5/sex) were exposed by nose only inhalation for 4 hours to nedocromil sodium dry powder (batch 2238T) at 1.02 mg/L air; controls (2/sex) were exposed to filtered air. Particle size was 1.48 μm MMAD, with 88.2% of particles < 3 μm . Blood samples (250 μL from tail vein) were obtained at -0.5, 1, and 4 hours relative to onset of dosing and at 0.25, 0.5, 1, 2, 4, and 24 hours relative to the end of dosing. The total inhaled dose is 98 mg/kg based on body weights of 349 g in males and 217 g in females, assuming minute volume = 0.8 L/min/kg and a total deposition factor of 50%.

Results: The plasma concentration vs time profile after single dose inhalation of nedocromil dry powder in rats is shown in figure 1, below. Plasma concentrations were similar in males and females. The C_{max} occurred immediately after the 4 hour inhalation period, averaging 2297 ng/mL in combined males and females. The AUC in combined males and females was 9912 ng-hr/mL (AUC/dose = 101 ng-hr/mL per mg/kg). Plasma concentrations decreased rapidly after the end of inhalation exposure. The initial $t_{1/2}$ measured from 0-4 hours after the end of dosing ranged from 1 to 2 hours and averaged 1.4 hours. The terminal $t_{1/2}$ was longer, about 4 hours.

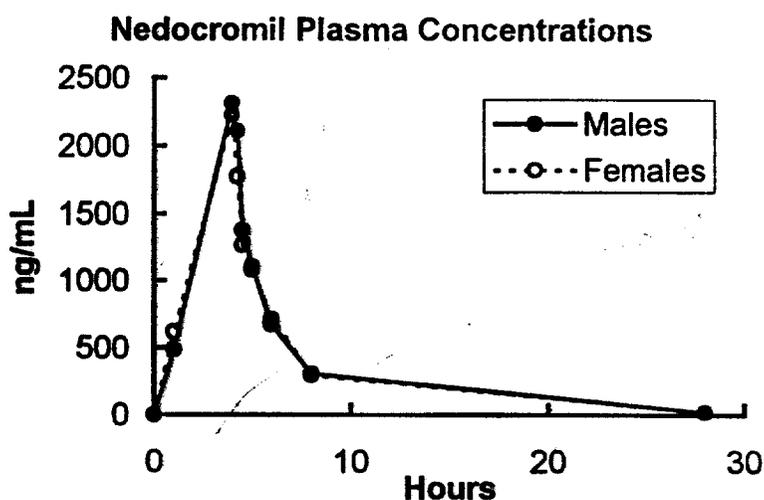


Figure 1. Nedocromil plasma concentrations after 4 hr dry powder inhalation exposure in rats.

Rat Single Dose MDI Inhalation Pharmacokinetics
Study SE 7618, Submitted 08/01/95 to IND :

Methods: Wistar rats (4/sex) were exposed by nose only inhalation for 3 hours to nedocromil sodium from MDIs (batch P3278) at 411 µg/L air; controls (4/sex) were exposed to filtered air. Particle size was not measured. Blood samples (250 µL from tail vein) were obtained before, and at 1, and 3 hours after the start of exposure, and at 0.25, 0.5, 1, 2, 4, and 24 hours after the end of exposure. The presented dose was calculated as 36 and 38 mg/kg, respectively, in males and females based on body weights and Guyton's formula for minute volume [$MV (mL) = 2.1 \times \text{body weight (g)}^{0.75}$] with no correction for deposition factor.

Results: Plasma concentrations were similar in males and females. The C_{max} occurred immediately after the 3 hour inhalation period, averaging 613 ng/mL in combined males and females. The AUC in combined males and females was 2231 ng·hr/mL (AUC/dose = 60 ng·hr/mL per mg/kg). Plasma concentrations decreased rapidly after the end of inhalation exposure. The initial $t_{1/2}$ measured from 0-4 hours after the end of dosing averaged 1.1 hours. Low levels of nedocromil (<2 to 16 ng/mL) were measured in control animals, suggesting that there was a minimal cross-contamination. Samples of distilled water from petri dishes in the exposure room also indicated low level contamination before and after treatment. The contamination is not serious enough to invalidate the results. If a total deposition factor of 50% is applied to this study, as in the previous study (SE7552) the relation of AUC/dose in this study (120 ng·hr/mL per mg/kg) is similar to that in the previous study (101 ng·hr/mL per mg/kg). The results from this study were used to estimate the high dose exposure for the rat inhalation carcinogenicity study.

Rat Fetal Transfer Study

Study SE 8993, Submitted 08/01/95 to INL

Methods: Distribution of radiolabeled ^{14}C -nedocromil was studied in 13- and 18-day pregnant Sprague-Dawley rats by autoradiography (n = 1 at day-13 and 2 at day-18) and scintillation counting (n = 3/time point at day-18) after a single intravenous dose of 5 mg/kg. Relative level of radioactivity on autoradiograms was scored on a grading scale.

Results: Tissue distributions by autoradiography and scintillation counting are summarized in tables 1 and 2, page 10. Liver and kidney were the major sites of accumulation in both dams and fetuses. There was some accumulation in fetal yolk sac. On gestation day-18 tissue levels by scintillation counting decreased markedly from 30 minutes to 6 hours post dose, although some activity was still detectable in fetal liver. By 24 hours, low activity was detectable only in maternal kidney. These results are qualitatively similar to those reported in study SE 6266 done by intravenous infusion, reviewed in the original NDA.

Table 1. Nedocromil Distribution by Autoradiography in Pregnant Rats

	Gestation Day 13		Gestation Day 18	
	30 min post Rx	30 min post Rx	30 min post Rx	24 hr post-Rx
Maternal blood	low activity	low activity	low activity	not detectable
Mammary gland	very low activity	very low activity	very low activity	not detectable
Ovaries	very low activity	very low activity	very low activity	not detectable
Placenta	very low activity	very low activity	very low activity	not detectable
Uterus	very low activity	very low activity	very low activity	very low activity
Amniotic fluid	not detectable	not detectable	not detectable	not detectable
Yolk sac	---	moderate activity	moderate activity	low activity
Fetus	not detectable	not detectable	not detectable	not detectable
Fetal liver	---	very low activity	very low activity	not detectable

Table 2. ¹⁴C-Nedocromil Levels (ng equivalents/g) in 18-Day Pregnant Rats

Tissue	30 minutes	6 hours	24 hours
Concentrations in Dam			
Plasma	220	ND	ND
Liver	1002	15	ND
Kidney	2706	54	30
Placenta	105	15	ND
Amniotic fluid	6	ND	ND
Concentrations in Fetus			
Whole fetus	20	ND	ND
Blood	ND	ND	ND
Liver	90	14	ND
Kidney	19	ND	ND

ND = not detectable

Elimination of Radiolabel in Milk (Rat, I.V.)

Study SE 9147, Submitted 03/24/94 to IND.

Methods: Single i.v. doses of 5 mg/kg ¹⁴C-nedocromil were administered to 4 female Sprague-Dawley rats, 12-14 days postpartum. Milk and plasma samples were collected at 0.08, 0.5, 1, 2, 4, 6, 24, and 48 hours after administration. Oxytocin (0.5 U/kg, i.m.) was given about 15-30 minutes before milk collections. Pups were removed about 1 hour before collection of milk and were returned afterward.

Results: Concentrations of nedocromil in plasma and milk are summarized in figure 2, page 11. The C_{max} in plasma was 3.4 µg/mL at 5 minutes after dosing; the C_{max} in milk was 1.0 µg/mL at 25 minutes after dosing. There was rapid biexponential elimination of nedocromil from plasma, with an initial t_{1/2} of 11 minutes and a secondary t_{1/2} of 2.3 hours. Nedocromil plasma concentrations were below the level of detection beyond 6 hours after dosing. Concentrations of nedocromil in milk were greater than those in plasma from 1 to 48 hours after dosing.

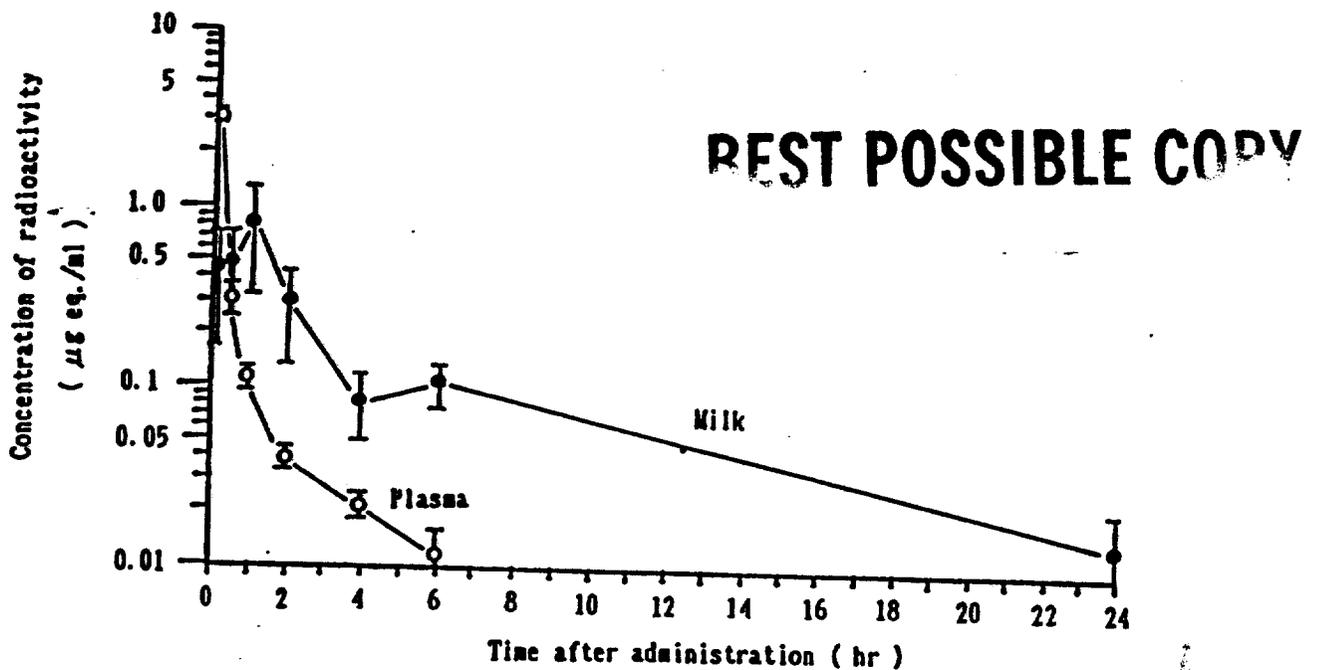


Figure 2. Nedocromil in milk and plasma of nursing rats given 5 mg/kg i.v. nedocromil.

Rat, Dog, and Human Serum Protein Binding
Study SE 9378, Submitted 08/01/95 to _

Methods: Serum and/or plasma binding studies of ^{14}C -nedocromil were carried out with fresh serum or plasma obtained from male and female rats, male dogs and male humans. Bound and unbound drug were determined by centrifuge ultrafiltration after 10 minutes incubation at 0.05, 0.1, and 1.0 $\mu\text{g}/\text{mL}$ nedocromil. Radioactivity was measured by scintillation counting.

Results: Results are summarized in table 3, page 12. In all species, percentage of drug bound decreased slightly as total drug concentration increased. Protein binding of nedocromil was minimally higher in female vs male rats. There was no significant difference between human plasma and serum in drug protein binding. There were significant differences in nedocromil binding among species, with the highest binding in human serum or plasma and the lowest in dog serum. These results are comparable to those determined previously by other techniques. These results have been used in the calculation of human free drug AUC for exposure ratios in rat and mouse carcinogenicity studies.

Table 3. Percent Nedocromil Binding to Serum or Plasma Protein In Vitro

Species	Total Nedocromil Concentration		
	0.05 µg/mL	0.1 µg/mL	1.0 µg/mL
Male rat serum	61.7 %	61.9 %	60.0 %
Female rat serum	64.1 %	62.7 %	62.9 %
Male dog serum	40.0 %	38.6 %	36.4 %
Male human serum	75.5 %	71.5 %	71.6 %
Male human plasma	75.6 %	74.0 %	74.5 %

Hepatic P450 Enzyme Induction In Rats (Intravenous)
Study SE 9380, Submitted 08/01/95 to IND

Methods: The effect of nedocromil on hepatic drug-metabolizing activity was studied after i.v. administration of 0.1, 1, and 10 mg/kg/day for 7 days in male Sprague-Dawley rats. The following endpoints were measured: body weight, liver weight, microsomal protein (mg/g liver), cytochrome P450 content, cytochrome b₅ content, NADPH-cytochrome c reductase activity, aminopyrine demethylase activity, aniline hydroxylase activity, and ethoxyresorufin deethylase activity.

Results: There were no toxicologically significant treatment-related effects on any of the measured endpoints. These results suggest that nedocromil has negligible tendency for induction of hepatic microsomal mixed-function oxidase activities.

Summary of Pharmacokinetics and Toxicokinetics

- In rats, inhalation of 98 mg/kg nedocromil dry powder resulted in a C_{max} of 2297 ng/mL and AUC of 9912 ng·hr/mL, with no difference between males and females.
- In rats, inhalation of 37 mg/kg (no correction for deposition factor) nedocromil MDI formulation resulted in a C_{max} of 613 ng/mL and AUC of 2231 ng·hr/mL, with no difference between males and females. AUC/dose is similar for both inhalation studies if a correction for deposition is applied to both.
- ¹⁴C-nedocromil administered, 5 mg/kg, i.v., to pregnant rats on gestation days 13 or 18 cleared rapidly and was distributed mainly to maternal kidney and liver with lower amounts detectable in fetal liver and yolk sac.
- ¹⁴C-nedocromil, 5 mg/kg, i.v., administered to nursing rats decreased to undetectable levels in plasma 6 hours after dosing; nedocromil concentrations in milk were greater than in plasma from 1 to 48 hours after dosing, indicating its excretion into milk.
- At nedocromil concentrations of 0.05 to 1.0 µg/mL, plasma or serum protein binding was 72-76% in humans, 60-64% in rats, and 36-40% in dogs, with slight decreases in protein binding at higher nedocromil concentrations.
- Administration of nedocromil 0.1, 1.0 or 10 mg/kg/day, i.v., for 7 days had no measurable effect on hepatic P450 enzyme activity.

TOXICOLOGY**ACUTE TOXICITY:****Acute p.o. and i.v. Toxicity in Rats**

Study SE 8384, submitted 06/11/92 to IND. volume 1, page 8-151

Methods: Male and female Wistar rats (5/sex dose) were administered nedocromil (lot # ZBB5R) in single p.o. or i.v. doses of 0, 1000, and 2000 mg/kg. The vehicle for p.o. dosing was distilled water; the vehicle for i.v. dosing was saline. Clinical signs and mortality were observed multiple times on the day of dosing and twice daily for 2 weeks, after which a gross necropsy was performed. Body weight was measured at -1, 0, 1, 3, 5, 7, 11, and 14 days after dosing. The study was carried out under Japanese GLP requirements.

Results: There were no deaths in any group. Loose feces were observed in all treated groups: 3/5 males and 3/5 females at 1000 mg/kg i.v., 3/5 males and 1/5 females at 2000 mg/kg i.v., 0/5 males and 2/5 females at 1000 mg/kg p.o., 3/5 males and 3/5 females at 2000 mg/kg i.v. The abnormal stools were observed immediately after and up to 3 hours after i.v. dosing, and from 90 minutes up to 6 hours after p.o. dosing. No abnormal signs were observed for the remainder of the 2-week observation period. Body weight gain was similar in all groups. There were no treatment related gross pathology findings.

Acute i.v. Toxicity in Adult Dogs

Study SE 8385, submitted 07/23/92 to IND vol. 2, pg. 8-387

Methods: Two dogs, 1 male and 1 female, were given 500, 1000 and 2000 mg/kg i.v. nedocromil in ascending doses on separate days with 6 days washout between doses. Clinical signs, heart rate, body temperature, body weight, and food intake were measured. A gross necropsy was performed 14 days after the last dose.

Results: Neither animal died. At 500 mg/kg nausea or vomiting, loose stool with mucus, urination, and increased water intake were observed. At 1000 mg/kg there was, in addition, bloody stool, lacrimation, and pale oral mucosa. At 2000 mg/kg there was, in addition, decreased spontaneous activity. These effects had returned to normal within 6 hours after dosing. There were no abnormalities noted at necropsy.

MULTIPLE DOSE TOXICITY:**Rat 13-Week Subcutaneous Toxicity Study**

Study SE 9898, submitted 04/03/96 to IND serial N158, volume 1, page 8-230

Study Dates: *In vivo* dates 30 MAY 89 to 7 SEP 89; report issued 13 APR 95

Testing Lab:

Test Article: Nedocromil sodium, lot 2618W, 93% purity

GLP: The study was accompanied by a signed GLP statement.

Methods: Wistar rats were assigned to the following treatment groups:

	Saline control	Nedocromil Sodium (mg/kg)		
Subcutaneous dose	5 mL/kg	100	320	1000
Number / sex	12	12	12	12

Observations included:

Clinical observation . three times daily

Body weight..... prestudy, weekly

Food consumption.... prestudy, weekly

Ophthalmology prestudy and 13-weeks

Clinical chemistry.... from tail vein under ether anesthesia at 13-weeks

Hematology from tail vein under ether anesthesia at 13-weeks

Urinalysis..... 16 hr collections in 6/sex/group in weeks 6 and 13

Drug levels Not measured

Necropsy..... terminal

Histopathology..... comprehensive list of tissues in control and high-dose groups, macroscopic lesions in all groups, target tissues (spleen and injection site) for all doses as suggested by examination of high-dose group.

Results: (Results are summarized in Table 4, page 15.)

Mortality: No treatment related deaths; one low dose female died after being dropped.

Clinical Signs: Treatment related clinical signs were soft or muddy feces, salivation, and sclerosis at the injection site. The incidence is indicated in table 4, pg. 15.

Body Weight: No toxicologically significant treatment-related effects.

Food Intake: No toxicologically significant treatment-related effects.

Ophthalmoscopy: No toxicologically significant treatment-related effects

Hematology: In males there were dose related decreases in red cell count, hemoglobin, and hematocrit, all statistically significant at the high dose (for clarity only red cell count is shown in the table). There were also increases in reticulocytes, platelets, and white cells. This would be consistent with hematopoietic stimulation in response to blood loss. In females the only statistically significant change was the increase in platelets.

Clinical Chemistry: Decreased total protein in high-dose males may also have been due to blood loss.

Urinalysis: Increased urine volume and decreased pH were noted in high-dose males. Statistical significance was not tested by the investigators.

Organ Weights: Relative spleen weight was increased in high-dose males.

Gross Pathology: No toxicologically significant treatment-related effects other than sclerosis at injection site noted under clinical signs.

Histopathology: Increased extramedullary hematopoiesis was seen in high-dose males and females. Dose related changes at the injection site in males and females included subcutaneous hemorrhage, inflammation, and fibrosis.

Table 4. Rat 13-Week Subcutaneous Toxicity Study

Nedocromil Dose (mg/kg)	Males				Females			
	0	100	320	1000	0	100	320	1000
Clinical Signs								
Soft or muddy feces	0/12	8/12	12/12	12/12	0/12	10/12	12/12	12/12
Salivation	0/12	5/12	7/12	9/12	0/12	3/12	8/12	9/12
Sclerosis at injection site	0/12	0/12	0/12	9/12	0/12	0/12	8/12	6/12
Hematology								
Red cell count ($10^4/\text{mm}^3$)	908	908	889	803	823	839	809	765
% Δ vs control group		0%	-2%	-12%		2%	-2%	-7%
Reticulocyte count (%)	14	12	16	28	18	14	16	27
% Δ vs control group		-14%	14%	100%		-22%	-11%	50%
Platelet count ($10^4/\text{mm}^3$)	91	96	98	114	81	89	87	107
% Δ vs control group		6%	8%	26%		10%	8%	32%
Leukocyte count ($10^3/\text{mm}^3$)	76	73	92	89	49	55	53	60
% Δ vs control group		-4%	21%	17%		12%	8%	22%
Total protein	6.82	6.67	6.6	6.45	6.54	6.53	6.63	6.38
% Δ vs control group		-2%	-3%	-5%		0%	1%	-2%
Urinalysis								
Volume (mL)	25	32	31	54	45	33	34	40
% Δ vs control group		27%	24%	113%		-28%	-24%	-13%
pH	8.42	8.42	7.83	6.67	8.42	8.17	8.42	8.25
Organ Weights								
Spleen (relative mg%)	168	160	175	193	205	217	197	214
% Δ vs control group		-5%	4%	15%		6%	-4%	4%
Histopathology								
Spleen:								
↑ extramedullary hematopoiesis	2/12	1/12	0/12	8/12	0/12	1/11	1/12	5/12
Injection site:								
subcutaneous inflammation	0/12	0/12	4/12	5/12	0/12	0/11	1/12	6/12
subcutaneous hemorrhage	1/12	1/12	12/12	12/12	1/12	0/11	11/12	12/12
↑ subcutaneous connective tissue	0/12	0/12	11/12	8/12	0/12	0/11	2/12	12/12

Highlighted values indicate statistically significant difference vs control group.

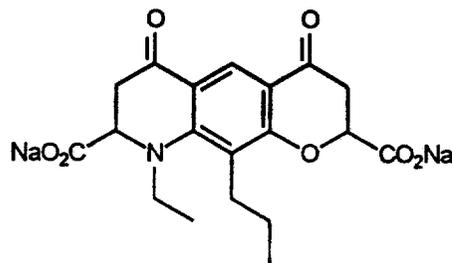
Summary of Toxicology

Acute Toxicity: In rats the minimal lethal dose after i.v. or p.o. administration was greater than 2000 mg/kg. Loose feces were observed at 1000 and 2000 mg/kg for up to 3 hours after i.v. dosing and up to 6 hours after p.o. dosing. No other toxic effects were observed, indicating no difference in toxicity between oral and i.v. administration. No mortality was observed in dogs at i.v. doses up to 2000 mg/kg.

Multiple Dose Toxicity: A 13-week subcutaneous toxicity study was done at higher doses than used in previous toxicity studies in an attempt to identify target organ toxicity. Soft stools and salivation were observed at doses from 100 to 1000 mg/kg/day. Increased urine volume and aciduria were seen in males at 1000 mg/kg/day. Local toxicity at the injection site consisted of subcutaneous hemorrhage, inflammation, and fibrosis at 320 and 1000 mg/kg. Other systemic changes, most prominent in males, appear to be in response to the local injury and blood loss; these changes include mild anemia with increased platelets, reticulocytes, and white cells, and increased spleen weight with microscopic evidence of increased extramedullary hematopoiesis. These are typical responses to blood loss.

SPECIAL TOXICITY STUDIES

Improvements in analytical methods have identified increased levels of two impurities in nedocromil inhalation solution. Structures are shown in figure 3, below.



Nedocromil Sodium

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REPRODUCTIVE TOXICITY

Rat Subcutaneous Teratology Dose-ranging Study

Study # SE9900, submitted 03 APR 96 to IND serial 158, vol. 2, pg. 8-476

Study Dates: Experimental - 26 DEC 89 to 21 JAN 90; report issued July 1992

Testing Lab:

Test Article: Nedocromil sodium, lot # 2618W, 99.0% pure on anhydrous basis

GLP: The study was an unaudited dose-ranging trial

Methods: Four groups of mated female Sprague-Dawley rats (n=8/group) were treated from day 7 to 17 post-coitum with subcutaneous doses of saline vehicle or 100, 320, and 1000 mg/kg nedocromil. The following observations were made after Cesarean section on day 20 post-coitum: number of corpora lutea, implantations, live fetuses, resorbed or dead fetuses, fetal weight, external fetal abnormalities, and sex ratio. Maternal observations included: clinical signs, daily body weight, daily food consumption, gross pathology, and placental weight.

Results:

EFFECTS IN DAMS (F₀):

Clinical signs: Loose or "muddy" stools on one or more days were observed in 4/8 at 100

mg/kg, in 7/8 at 320 mg/kg, and in 8/8 at 1000 mg/kg.

There were no significant treatment-related effects on: body weight, food intake, gross pathology, number of corpora lutea and placental weight.

EFFECTS IN FETUSES (F₁)

There were no significant treatment-related effects on: number of implants, number of live fetuses, early fetal deaths, late fetal deaths, sex ratio of fetuses, body weight of fetuses, and number of fetuses with external abnormalities.

Comment: Based on this dose-ranging study, the same dose levels (100, 320, and 1000 mg/kg) were chosen for the definitive rat teratology study.

Rat Subcutaneous Teratology and Developmental Study

Study # SE9901, submitted 03 APR 96 to IND serial 158, vol. 2, pg. 8-540

Study Dates: Experimental - 23 MAR 90 to 22 AUG 90; report issued July 1992

Testing Lab:

Test Article: Nedocromil sodium, lot # 2618W, 99.0% pure on anhydrous basis

GLP: The study was accompanied by a signed GLP statement.

Methods: Four groups of mated female rats were treated from day 7 to 17 post-coitum with s.c. doses of saline vehicle or 100, 320, and 1000 mg/kg nedocromil. In each group 13 dams were allocated for natural birth and 24 for cesarean section on day 20 post-coitum. Natural birth litters were culled to 4/sex/litter on day 4 post partum. At weaning, 1/sex/litter were used for behavior tests and 2/sex/litter were used for fertility tests.

Observations on Dams (F₀):

Clinical observation ... TID during dosing, BID until delivery, daily thereafter
 Body weight..... gestation days 0, 4, 7-delivery, 3-4 day intervals post partum
 Food consumption..... gestation days 0, 4, 7-delivery, 3-4 day intervals post partum
 Gross pathology gestation day 20 (cesarean); post partum day 22 (natural birth)
 Corpora lutea terminal
 Implantation sites terminal
 Placenta weight terminal

Observations on Cesarean Fetuses (F₁) at Delivery:

Fetal weight all
 Early & late deaths all
 Sex all
 External exam all
 Visceral exam ~1/3 of those without external abnormalities
 Skeletal exam ~2/3 of those without external abnormalities

Observations on Natural Delivery Pups (F₁), all at birth or survivors post-culling:

Delivery live & dead pups counted, weighed, sexed, and examined externally.

Lactation.....clinical observation daily; body weight on days 4, 7, 11, 14, 18, and 22 post partum; developmental milestones (ear unfolding on day 4, hair and tooth eruption on days 11 and 14, eye opening on days 14 and 18); early behavior screen (righting, grasp reflex etc.) on day 15; necropsy on day 22 for those not kept for post-weaning observation.

Post-weaning

(Behavior).....clinical observation daily; body weight weekly; sensory function at 5 weeks; open field test at 6 weeks; conditioned avoidance test at 8 weeks; necropsy and skeletal abnormalities by soft X-ray at 10 weeks.

(Reproduction)....genital development (descent of testes at day 28 and 35, penis development at day 49 and 56, opening of vagina on days 42 and 49); estrous cycle (daily vaginal smears in weeks 8-9); mating in weeks 10-11; body weight of mated females at 3-4 day intervals during gestation, cesarean section on gestation day 20 with confirmation of pregnancy and number of corpora lutea, and microscopic examination of pituitary, ovaries and uterus in nonpregnant females; gross and microscopic examination and organ weight of male reproductive organs at 18 weeks.

Observations on Cesarean Fetuses (F2) at Delivery:

Same as for F1 cesarean fetuses except that visceral and skeletal exams were not done.

Results:

EFFECTS ON DAMS (F0):

Clinical signs: The signs tabulated below were noted "sporadically" from gestation days 7-17.

	100 mg/kg	320 mg/kg	1000 mg/kg
Soft feces	"about half"	"many"	"many"
Decreased activity	"a few"	"many"	"many"
Salivation	one	"a few"	"many"

For cesarean and natural delivery groups there were no significant treatment-related effects during gestation, lactation, or at termination on: body weight, food intake, gross pathology, number of corpora lutea, placental weight, and duration of gestation

EFFECTS ON CESAREAN FETUSES (F1):

There were no significant treatment-related effects on: number of implants, number of live fetuses, early or late fetal deaths, sex ratio, body weight, and visceral or skeletal abnormalities.

External abnormalities: (Among cesarean deliveries there were no anomalies in the control group vs 3, 1, and 2 anomalies, respectively, in low- mid- and high-dose groups. Because there was no dose response and the differences were not statistically significant they should not be considered treatment-related. There were no external abnormalities in any of the natural live births.)

EFFECTS ON NATURAL DELIVERY PUPS (F₁):

Delivery: There were no treatment effects on litter size, live births/stillbirths, body weight, sex ratio or external anomalies.

Lactation: During lactation there were no treatment effects on mortality, body weight, developmental milestones (unfolding of ears, opening of eyelids, etc.), early behavior at 15 days (righting reflex, auditory startle etc.), or gross pathology at necropsy on day 22.

Post-weaning:

Clinical Signs: No effect.

Body Weight: Weight gain in treated females was slightly decreased compared to the control group ($P < 0.05$ on day 70 at 320 mg/kg and from days 49 to 70 at 1000 mg/kg). Final body weights at day 70 are summarized below:

	Control	100 mg/kg	320 mg/kg	1000 mg/kg
Body weight (g)	264 ± 26	251 ± 18	247 ± 16	243 ± 20
%Δ vs control	---	4.9 %↓	6.4 %↓	8.0 %↓

In pregnant F₁ dams body weight gain during gestation was slightly greater than in controls so that at the end of gestation there were no longer any significant differences in body weight. There was no effect on body weight in males.

There were no significant treatment related effects on:

Genital Development

Sensory Function at 5-weeks

Open Field Behavior at 6-weeks

Conditioned avoidance response at 7 to 8-weeks

X-ray skeletal exam at 10-weeks

Estrous cycle length at 8 to 11-weeks

Numbers of males and females mating, impregnated, and pregnant

Male reproductive organ weight

Number of corpora lutea in pregnant dams

Placental weight of pregnant dams

EFFECTS ON CESAREAN FETUSES (F₂):

There were no significant treatment-related effects on:

Number of implants

Number of live fetuses

Early fetal deaths

Late fetal deaths

Sex ratio of fetuses

Body weight of fetuses

External abnormalities (visceral and skeletal exam not performed)

Summary of Reproductive Toxicity

Nedocromil was tested in a rat teratology dose-ranging study at s.c. doses of 100, 320 and 1000 mg/kg/day. Dose related soft feces were observed in all treatment groups. No other maternal effects and no fetal effects were observed up to 1000 mg/kg/day.

Nedocromil was tested in a definitive three generation rat teratology study at s.c. doses of 100, 320 and 1000 mg/kg/day. The only maternal effects in F₀ dams were dose related soft feces, decreased activity, and salivation. There were no effects on F₁ fetuses or pups up to weaning. In F₁ females whose mothers had received 320 or 1000 mg/kg nedocromil, there was a small but statistically significant decrease in body weight gain from weaning through mating (6.4 and 8% decrease, respectively). The difference in weight gain did not persist through gestation and there were no additional effects on F₁ dams or F₂ fetuses.

GENETIC TOXICITY***In Vivo* Mouse Micronucleus Test**

Study # SE9873, submitted 03 APR 96 to IND serial 158, vol. 1, pg. 8-93

Study Dates: Experimental - 06 JUN 95 to 11 AUG 95, report issued 09 OCT 95

Testing Lab:

Test Articles: Nedocromil sodium(batch 3650E)

GLP: The study was accompanied by a signed GLP statement.

Methods: CD-1 mice were assigned to the following treatment groups:

	Saline	mitomycin C	Nedocromil sodium		
Dose	20 mL/kg	12 mg/kg	500 mg/kg	1000 mg/kg	2000 mg/kg
Route	s.c.	p.o.	s.c.	s.c.	s.c.
No. examined at 24 hr.	5/sex	5/sex	5/sex	5/sex	5/sex
No. examined at 48 hr.	5/sex	---	---	---	5/sex

Drug or control treatments were given as a single dose and bone marrow smears were obtained from the femurs at 24 or 48 hours after treatment. The stained smears were

randomized and coded slides examined for polychromatic (PCE) and normochromatic (NCE) erythrocytes. One smear from each animal was scored for the frequency of micronucleated PCEs in 2000 cells. The ratio of PCE/NCE, determined from examination of 1000 erythrocytes per animal, was used as a measure of bone marrow toxicity. Data were analyzed by Wilcoxon's nonparametric ranked sum test. Criteria for a positive response were a statistically significant ($P < 0.01$) increase in the incidence of micronucleated PCEs, for at least one sampling time, compared to the concurrent negative control group, and with individual or group mean values of the treated group exceeding the historical control range.

Results: The incidence of micronucleated PCEs in nedocromil treated groups (1.1 to 1.8 per 2000) did not differ significantly from the negative control groups (0.9 per 2000 at 24 hr.; 0.8 per 2000 at 48 hr.). The positive control, mitomycin C, caused a highly significant increase in the incidence of micronucleated PCEs (52 per 2000). Neither nedocromil nor mitomycin C caused a statistically significant decrease in the ratio of PCE/NCE. Thus, under the conditions of this test, there was no evidence of clastogenic potential for nedocromil tested to an accepted limit dose of 2000 mg/kg.

Comment: The previous mouse micronucleus test with nedocromil (study # SE 5868) was done at a high dose of 400 mg/kg, which does not meet current standards for high dose selection based on toxicity or limit dose. The present study (SE 9873) showed nedocromil to be negative in the mouse micronucleus assay up to an accepted limit dose of 2000 mg/kg (see OECD guidelines for the testing of chemicals).

OVERALL SUMMARY AND EVALUATION

The preclinical pharmacodynamic, pharmacokinetic, and toxicologic properties of nedocromil have been extensively studied and documented in NDA 19-660 for the MDI 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 new studies submitted after approval of NDA 19-660 that are covered in the present review.

Pharmacology

Nedocromil inhibits a variety of cellular inflammatory processes that may contribute to allergic asthma. It has been shown to inhibit the recruitment and activation of inflammatory cells including neutrophils, and eosinophils; it inhibits release or production of histamine and lipid derived mediators (e.g. prostaglandins and leukotrienes) from mast cells. In a variety of *in vivo* animal models, nedocromil inhibits bronchoconstriction, and inflammatory responses secondary to antigen-challenge. The cellular mechanism(s) of nedocromil action have not been fully defined but its effects on allergic responses are similar to those of the structurally related cromolyn sodium. Nedocromil has no direct

relaxant effect on bronchial smooth muscle, and does not interact directly with adrenergic, glucocorticoid, histamine, or leukotriene receptors.

In addition to these anti-allergic actions, the pharmacology studies covered in this review demonstrate that nedocromil can interfere with effects believed to be mediated by neuronal release of tachykinins. Nedocromil acted synergistically with salbutamol, to inhibit tracheal vascular leakage after vagal stimulation in rats. In guinea pigs, nedocromil inhibited cough induced by citric acid, cough and bronchoconstriction induced by capsaicin, and bronchial contraction induced by stimulation of non-adrenergic non-cholinergic (NANC) nerves. In rabbits, nedocromil caused a chloride channel mediated depolarizing blockade of isolated vagal fibers, inhibited NANC mediated contractions of isolated iris, and inhibited the ability of substance-P to potentiate contractions of isolated rabbit trachea elicited by preganglionic parasympathetic stimulation. In allergic sheep, nedocromil decreased the sensitivity to bronchoconstriction induced by metabisulfite, which is believed to be mediated via irritation of sensory nerves. An additional unrelated action of nedocromil was the inhibition of PAF-induced airway responses in allergic sheep. The relevance of these actions to the clinical efficacy of nedocromil is unknown, but the studies do support the new statements in the proposed labeling that "nedocromil sodium inhibits neuronally mediated responses in a variety of *in vitro* and *in vivo* tests" and "nedocromil sodium also reduced PAF-induced airway responses when administered by inhalation with a nebulizer in another model system".

Pharmacokinetics

Previous studies have shown that nedocromil 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 i.v. administration tissue distribution of nedocromil is mainly in blood, kidney, liver, and intestinal tract. Studies previously reviewed in NDA 19-660 and new studies cited in NDA 20-750 show that i.v. nedocromil administered to pregnant rats was distributed at low levels to the fetal liver and yolk sac and i.v. nedocromil administered to lactating rats was excreted in milk. Low levels of nedocromil were detected in milk up to 48 hours after dosing. Plasma protein binding of nedocromil 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. A new protein binding study was cited that compared nedocromil binding in human serum vs plasma and rat serum binding for male vs female. There were no significant differences for serum vs plasma or male vs female. Nedocromil is excreted unchanged, no metabolites have been identified in mouse, rat, rabbit, or dog. A new study shows that 1-week i.v. administration of nedocromil had no effect on hepatic P450 enzyme activity. Nedocromil is rapidly eliminated from plasma with clearance rates of >300 mL/min/kg in mouse, ~70 mL/min/kg in rat, ~20 mL/min/kg in rabbit, and ~30 mL/min/kg in dog. The major route of excretion varies widely among species with a ratio of urinary:biliary % excretion of 30:70 in mouse, 45:55 in rat, 95:5 in rabbit, and 60:40 in dog. The species with the higher proportion of biliary excretion

(mouse and rat) have a more rapid clearance than the species with the higher proportion of urinary excretion (rabbit and dog).

Toxicology

No histologic target organ toxicity has been reproducibly identified for nedocromil. The most consistent signs of toxicity have been gastrointestinal disorders including salivation, emesis, and loose stools.

Acute Toxicity: Previous studies (2 males per dose) showed that the acute maximum nonlethal dose of nedocromil in rats and mice by oral or subcutaneous routes was greater than 4000 mg/kg; by the i.v. route the maximum nonlethal dose in rats and mice was 2000 mg/kg. At 4000 mg/kg, i.v. all animals died, with collapse, ataxia and convulsions preceding death; cause of death was not defined. An additional study cited in NDA 20-750 using larger groups of male and female rats (5/sex/dose) measured oral and i.v. toxicity at 1000 and 2000 mg/kg. No deaths were observed up to 2000 mg/kg. Loose feces were observed at 1000 and 2000 mg/kg by either p.o. or i.v. administration. Intravenous infusion up to 4 mg/kg/minute (240 mg/kg) in anesthetized cats caused no visible symptoms, with peak plasma levels reaching 300 µg/mL. Acute i.v. doses of 500, 1000, and 2000 mg/kg were tested in dogs. There were no deaths. The gastrointestinal system was the main target of toxicity, with nausea, vomiting, and loose stools with mucus at doses of 500 mg/kg and above. Young dogs were less sensitive to these effects. In 3-week old dogs acute i.v. nedocromil was well tolerated at 1000 and 2000 mg/kg i.v., with pale mucosa at both doses and one incidence of emesis at 1000 mg/kg (review of NDA 19-660 by Y.S. Choi, 6/18/96). It is likely that the pale oral mucosa in dogs is a manifestation of hypotension; nedocromil elicits hypotension via activation of the Bezold-Jarisch reflex in dogs (original review of NDA 19-660 by C. Oberlander, 5/29/87).

Multiple Dose Inhalation Toxicity: In 3- and 6-month rat inhalation studies with the MDI formulation, there was 16-26% less body weight gain at the high dose of 30 mg/kg. There were no consistent target organ effects other than occasional pale areas in the lung with increased incidence of distended macrophages in the lung. In a 2-year rat inhalation carcinogenicity study there was a statistically significant trend for increased survival in treated rats; final body weight at the high dose of 24 mg/kg was minimally decreased (4-6%). Focal areas of distended macrophages were found in vehicle and treated groups. The distended macrophages in the several studies were attributed to sorbitan trioleate in the vehicle.

In dogs, a 3-month inhalation study at 1 and 6 mg/kg found loose feces at both doses and salivation at the high dose, with no other drug related effects. A 6-month combined inhalation/subcutaneous study in dogs at 5, 20, and 40 mg/kg found dose-related salivation and head shaking. Two high-dose male dogs had brief convulsive episodes on

several occasions. A 12-month combined inhalation/subcutaneous study in dogs at 3, 10, and 20 mg/kg found dose-related salivation; frequent head-shaking/tremors was seen in one control and one high-dose animal, with occasional episodes in other animals from all groups; convulsions were not observed.

Multiple Dose Toxicity by Other Routes: Other multiple dose toxicity studies were conducted by a variety of routes. Intravenous studies included: a 14-day dog study at 8 and 80 mg/kg, with ataxia and local effects at the injection site at both doses, a 4-week rat study (males) with no drug related effects up to the high dose of 120 mg/kg, a 4-week juvenile dog study with sporadic salivation, retching, and emesis in treated groups and infiltration of the portal area of liver at mid and high doses of 320 and 1000 mg/kg (NDA 19-660, reviewed by Y.S. Choi, 18 JUN 96). Subcutaneous studies included: a 1-month rat study with no drug related toxicity up to the high dose of 180 mg/kg, a 1-month neonatal rat study with no drug related toxicity up to the high dose of 100 mg/kg, a 56-day weanling rat study with no drug related toxicity up to the high dose of 100 mg/kg, a 13-week rat study with loose stools at doses of 100 mg/kg and higher and toxicity at 320 and 1000 mg/kg secondary to hemorrhage at the injection site. Intranasal studies included: a 1-month rabbit study with no local toxicity up to the high dose of 119 mg/kg, a 6-month dog study with no local toxicity but increased emesis at the high dose of 7 mg/kg and a single transient convulsive episode in one high-dose dog. Ocular studies included: 7-day and 3-month rabbit studies with no drug-related eye irritation at concentrations up to 4%; a 6-month rabbit study with no eye irritation at concentrations up to 4%, some observations of yellow coloration of the cornea, and deaths in one control, one low-dose, and two high-dose animals. The deaths were associated with gastrointestinal symptoms attributed to gastrointestinal infection. A repeat 6-month rabbit study with high systemic exposure reported deaths in 2/20 at 3.2 mg/day ($C_{max} = 98$ ng/ml) and in 2/22 at 6.4 mg/day ($C_{max} = 201$ ng/mL). For comparison, clinical C_{max} after nebulized nedocromil is 2.5-5 ng/mL. The deaths were associated with loose mucus-containing stools. The deaths in the rabbit studies may be fortuitous incidents of gastrointestinal infection, which is common in rabbits but, due to the gastrointestinal effects of high dose nedocromil in other species, a drug-related effect cannot be completely ruled out. The yellow coloration of the cornea reported in the previous study was not confirmed in the repeat study.

Previous studies of nedocromil showed that it has a relatively low order of toxicity and no specific target organ toxicity was consistently identified. Additional acute and multiple dose studies cited in NDA 20-750 suggest that the gastrointestinal tract is the most consistent target, with loose feces, diarrhea, salivation and emesis in various species. These preclinical findings are consistent with the increased incidence of diarrhea found in clinical studies (3.6% with nedocromil vs 1.8% with placebo, $P < 0.05$, reported under adverse events in the labeling). Nedocromil can interact with chloride channels in sensory neurons (Eur J Pharmacol 221:175, 92) and in endothelial cells (study T48A); it is possible that nedocromil has an interaction with the chloride channels that regulate water

balance in the intestinal tract. No histopathological effect of nedocromil has been identified other than local hemorrhage at the s.c. injection site. The original reviewer concurred with the sponsor's assessment that head shaking, tremors, and convulsions in dogs were not specific drug effects but might be attributed to a combination of the stressful dosing procedure, high concentrations of CFC propellant, and activation of the Bezold-Jarish reflex in dogs, with hypotension and decreased cerebral blood flow. The bad taste of nedocromil, frequently observed in clinical studies, might also contribute to behaviors such as head shaking and salivation. The lack of convulsions in the 12-month dog study and in a 1-month intravenous study up to 1000 mg/kg suggest that this is not a direct toxicological effect of nedocromil. If the effect were considered drug-related the NOEL for convulsions in the 6-month dog study was 20 mg/kg, approximately 23 times the adult dose of nedocromil on a mg/kg basis).

Carcinogenesis

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 MDI formulation (approximately 4 times the maximum recommended inhalation dose in adults on a mg/m² basis). This was determined to be the maximum feasible inhalation dose. In the CAC report dated 10/17/91 the rat inhalation study was found to be valid and adequate. Nedocromil plasma levels were not measured in the rat inhalation carcinogenicity study. Extrapolating from a separate PK study (SE 7618), and assuming 70% protein binding (average from all rat protein binding studies), the AUC for free nedocromil is estimated at 430 ng·hr/mL. This is approximately 60 times the daily human AUC for unbound nedocromil, based on an AUC of 10 ng·hr/mL per dose, times 4 daily doses, with 82% protein binding. No dose correction for deposition fraction was used either in the inhalation carcinogenicity study or the inhalation PK study. The exposure ratio in the labeling should be expressed in terms of estimated AUC for free nedocromil.

No increased tumor incidence was found in a 2-year mouse dietary carcinogenicity study at a maximum dose of 180 mg/kg (~15 times the maximum recommended inhalation dose in adults on a mg/m² basis). However, the high dose was not near a maximum tolerated or maximum feasible dose for dietary intake. The dose was originally picked as a high multiple (~500-fold) of the clinical MDI dose on a mg/kg basis. Systemic exposure in the mouse study was estimated to be ~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, 08 APR 97). 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. However, in accordance with one of several options suggested by the executive CAC (13 MAY 97), 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 based on the observations that there was no indication of carcinogenic potential in the rat study or at the doses tested in mice, because the drug is not metabolized in humans or animals there is no potential for activation to carcinogenic metabolites, no genotoxic effects have been identified in an appropriate battery of tests, and no histopathological end organ toxicity has been identified. Thus, the sum of information available suggests a minimal carcinogenic potential, and the drug can be approved with a disclaimer in the label indicating that carcinogenic potential may not have been fully explored in mice.

Reproduction

In NDA 19-660, no effects of nedocromil on fertility or fetal development were identified in the following subcutaneous reproduction and developmental studies, all using a high dose of 100 mg/kg: mating, fertility, and early embryonic development studies (segment I) in rats and mice; teratogenicity studies (segment II) in rats and rabbits; a pre- and postnatal development study (segment III) in rats. None of these studies elicited maternal toxicity. A new three generation study in rats used s.c. doses of 100, 320 and 1000 mg/kg. This study showed no toxicologically significant effect of nedocromil on the F₁ or F₂ generations, with mild dose-related maternal toxicity of salivation, soft feces, and decreased activity. A mild unexplained decrease in weight gain in F₁ females only, from lactation up to mating, was not sustained during gestation in the F₁ dams and does not appear to be toxicologically significant.

Genetic Toxicity

Nedocromil was negative in a standard battery of genetic toxicity tests including the Ames Salmonella assay (up to 5 mg/plate), mitotic gene conversion in *Saccharomyces cerevisiae* (up to 2 mg/mL), mouse lymphoma forward mutation (up to 10 mg/mL), mouse micronucleus assay (up to 400 mg/kg), and metaphase analysis of human lymphocytes (up to 5 mg/mL). The previous mouse micronucleus test does not meet current criteria of MTD or a limit dose of 2000 mg/kg. A new *in vivo* mouse micronucleus at doses of 1000 and 2000 mg/kg found no bone marrow toxicity and no effect on micronucleus frequency. This test meets current standards for an appropriate high dose. The maximum concentrations used in the original *in vitro* tests are also acceptable by current guidelines.

Impurities

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page(s) of trade

secret and/or

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RECOMMENDATIONS

- The extensive preclinical testing conducted in support of NDA 19-660 (MDI formulation) and the additional studies covered in this review support the safe use of nedocromil aerosol solution for nebulization.
- Preclinical aspects of the labeling are reviewed below and specific changes are recommended.

Labeling Review

Cellular and Animal Pharmacology: The sponsor has included two new preclinical pharmacology claims in the labeling. 1) "Nedocromil sodium has been shown to inhibit neuronally mediated responses in a variety of *in vitro* and *in vivo* tests"; and 2) Nedocromil sodium also reduced PAF-induced airway responses when administered by inhalation with a nebulizer in another model system". Both claims are supported by the studies covered in the pharmacology section of this review. The phrase "in another model system" should be changed to specify that studies were done in allergic sheep. Another sentence stating that nedocromil reduced microvasculature leakage when administered "in a model system", should be changed to specify that studies were done in sensitized guinea pigs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The sponsor has adopted the carcinogenesis labeling suggested by the Division in our letter dated June 24, 1997 and discussed in a teleconference on July 11, 1997. The labeling has been changed to express the exposure in the rat and mouse carcinogenesis studies in terms of AUC for free drug. As suggested by the executive CAC in their discussion of nedocromil on May 13, 1997, a statement has been added that the doses used in the mouse study may not have been high enough to fully evaluate the carcinogenic potential in this species. Minor changes need to be made in the exposure ratios for fertility studies to reflect the new rounding conventions adopted by the Division.

Pregnancy: Minor changes need to be made in the exposure ratios to reflect the new rounding conventions adopted by the Division. A statement should be added that nedocromil crosses the placenta in pregnant rats.

Nursing Mothers: A statement should be added to indicate that nedocromil was excreted into the milk of nursing rats (study SE9147).

Overdosage: The proposed labeling does not include preclinical doses to characterize the acute toxicity of nedocromil (e.g. LD₅₀, maximum non-lethal doses, etc.), this should be added to the labeling. The proposed labeling indicates that nedocromil caused head shaking, tremor, and convulsions in dogs after inhalation or combined inhalation and s.c. dosing. This is accompanied by qualifying statements that nedocromil does not cross the blood brain barrier and had no effect in tests designed to evaluate CNS function. These statements were included in the previous Tilade MDI labeling. Because these findings occurred in multiple dose 6 month (study SE 5805) and 12 month (study SE 6079) studies and not in acute toxicity studies, they should not be included in the overdosage section according to current Division practice. Acute intravenous administration of nedocromil at 2000 mg/kg i.v. in 3-week old dogs caused no serious toxicity (study SE 9253 see review of NDA 19-660 reviewed by Y.S. Choi, 18 JUN 96). Acute intravenous administration of nedocromil at ascending doses from 500 to 2000 mg/kg i.v. in adult dogs caused vomiting, urination, loose stools, pale oral mucosa, lacrimation, and salivation, but tremors, head shaking or convulsions were not observed (study SE 8385).

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PURGED

DRAFT LABELING

JUN 17 1997

**DIVISION OF PULMONARY DRUG PRODUCTS
PHARMACOLOGY REVIEW OF ENVIRONMENTAL ASSESSMENT**

NDA No. 20-750 Serial No. N000 (BZ)

Submission date: 11 FEB 97

Reviewer: W. Mark Vogel, Ph.D.

Review Completed: 18 JUN 97

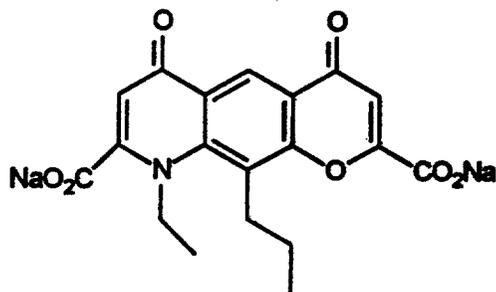
Information to be Conveyed to Sponsor: Yes (), No (✓)

Sponsor: Rhone-Poulenc Rorer, Collegeville, PA

Names: *Proprietary Name:* Tilade® Nebulizer Solution
Established Name: Nedocromil sodium inhalation solution
Code Names:

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

Structure:



Chemical Formula: C₁₉H₁₅NNa₂O₇
Molecular Weight: 415.31
CAS No.: 69049-74-7
Class: Anti-allergic
Route: Inhalation

Indication: Mild to moderate asthma in patients aged 2 and older

Dosage: The maximum recommended dose in adults and children 2 years of age and older is the contents of one ampule (11 mg) administered by nebulization four times a day (total daily dose = 44 mg).

Clinical Formulation: TILADE Nebulizer Solution is a clear yellow solution supplied in a low density polyethylene plastic unit dose ampule with 12 ampules per foil pouch. Each ampule contains 11 mg nedocromil sodium in 2.2 mL of aqueous solution made isotonic with sodium chloride. Hydrochloric acid is used to adjust the pH within the range 4.0 to 5.5.

ENVIRONMENTAL ASSESSMENT

Based on the physicochemical properties of nedocromil it is expected to enter the aquatic environment. A fifth year market projection for the United States was conducted for all nedocromil containing products, including the Nebulizer Solution. Based on this projection, the Expected Introduction Concentration (EIC) into the aquatic environment is calculated as 1.19×10^{-5} ppm or 11.9 ppt for all nedocromil drug substance. This level is far below the 1 ppb level. Therefore, the Tier 0 approach is claimed for this NDA and no further data or information is provided for format items 7, 8, 9, 10, 11, and 14.

RECOMMENDATION

Items 7, 8, 9, 10, 11, and 14 of the environmental assessment for NDA 20-750 are acceptable, based on a Tier 0 approach

W. Mark Vogel 6/17/97

Mark Vogel, Ph.D., Pharmacologist

Cheryl Josephson June 17, 1997

Original NDA 20-750
c.c. HFD-570/Division File
HFD-570/C. Kim
HFD-570/B. Gallaresi
HFD-570/W.M. Vogel

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