CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20750

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

AUG 7 1997

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-750	SUBMISSION DATE:
Nedocromil sodium	09/30/96
	05/12/97
	06/02/97
BRAND NAME:	06/10/97
Tilade 0.5% Nebulizer Solution	06/23/97
	07/25/97

SPONSOR: Rhône-Poulenc Rorer

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: A New Formulation of An Approved Drug Code: 3S

TITLE: "Review of Human Pharmacokinetics and Bioavailability Study For Tilade 0.5% Nebulizer Solution"

SYNOPSIS:

Previously, Tilade Inhaler aerosol MDI for nedocromil sod. (2 mg/actuation) was filed under NDA 19-660 by Rhône-Poulenc Rorer (RPR). The NDA was reviewed and approved by the Agency on 12/30/92. It is indicated for the management of mild to moderate bronchial asthma in patients aged 12 years and older. It is not indicated for the reversal of acute bronchospasm. A pediatric supplement was submitted later and approved on 03/05/97 to support the extension of the age of patients from 12 down to 6 years old.

On 09/30/96, RPR submitted Tilade (nedocromil sod.) 0.5% Nebulizer Solution (N.S.) to the Agency for review that was filed under NDA 20-750. For this NDA, the same indication as for Tilade inhaler aerosol MDI is being sought and the recommended starting dose is 1 amouple administered by nebulizer TID or QID for patients 2 years and older.

Submitted under Human Pharmacokinetics/Bioavailability section of NDA 20-750, were 23 pharmacokinetic/bioavailability (PK/Bio) studies. Thirteen were reviewed previously and are cross-referenced to NDA 19-660. Therefore, the rest of 10 PK/Bio studies are submitted and reviewed under this NDA. Six studies are considered to be pivotal.

Some basic PK parameters obtained from this NDA are summarized here. Mean (±standard deviation; SD) total plasma clearance (CL) and terminal half-life ($T_{1/2}$) of nedocromil in healthy adults after intravenous (IV) infusion are 797 ± 186 ml/min and 31.6 (± 7.6) min, respectively, and they are consistent with those obtained previously. As compared to an IV dose, the absolute bioavailability (F_{abs}) for a 4-mg dose of Tilade Inhaler aerosol MDI are 6% and 8%, based on the mean area under the

curve (AUC) and urinary excretion data. However, those for a nominal dose of 20 mg N.S. could not be determined quantitatively due to the fact that the residual volume of inhalation solution being left in the device after 5-min inhalation was not known and/or taken into consideration.

The results of previous in vivo metabolism study of nedocromil (NDA 19-660) showed that after an IV infusion of ^{14}C nedocromil, 1) urinary excretion of radioactivity accounted for 64% of the dose (up to 3 days), 2) 97% of the above excreted radioactivity was collected within 4 hr post dosing, 3) fecal excretion accounted for the rest of 36% up to 6 days, and 4) nedocromil is not metabolized which is consistent with animal data. Furthermore, results of previous in vitro study showed that 1) around 6% of ^{14}C-nedocromil was associated with packed RBC fraction, 2) the plasma protein binding (f_b) was about 89%, and 3) f_b for rabbit, dog, and mice were around 80, 70, and 40%, respectively.

A single-dose PK study investigated a 10-mg dose of Tilade N.S. in 10 healthy volunteers using three different nebulizers, **Henley Fan-Jet, Medix,** and **Pulmosonic.** The results showed that the above three nebulizers gave comparable mean peak plasma levels (C_{max}) and area under the curve (AUC) when the Tilade N.S. was not diluted. Dilution (x 2) gave significantly higher mean C_{max} and AUC values. Other two single-dose studies, however, employed only one type of nebulizer in one study and the results showed that as compared to the same dose of Tilade aerosol MDI, **Millicon** nebulizer gave lower mean C_{max} and AUC values, while **Omron** nebulizer gave higher mean C_{max} and AUC values. Large variation in nedocromil C_{max} or AUC values among studies could be due to the variability in delivery by different nebulizer devices.

The to-be-marketed formulation was used in most of the clinical trials and PK/Bio studies. Dose range from 5 to 80 mg was investigated in a supportive study and it appears to be proportional based on mean C_{max} and AUC_{0-24} (extrapolation from 4 to 24 hr) values. Small numbers of male and female subjects were employed in most of the studies and no major gender differences were found.

PK and pharmacodynamic (PD) relationship was investigated in two studies using a small number of patients for exercise-induced bronchospasm (EIB). Doses between 2 and 80 mg and a placebo were given via **Wright** nebulizer. The results showed that 1) all active treatments gave a statistically significantly greater % protection compared to control ($P<0.01$), 2) no differences among the active treatments were found, 3) their effects were similar to that of a 4-mg dose of Tilade aerosol MDI (during the screening test), and 4) nedocromil mean C_{max} values were found to be increased nearly double after exercise which could be due to an increase in absorption of the drug from the lungs as a result of increased cardiac output to the lungs. However, the protection effects seemed to be decreased with time after repeated exercises.

Single-point plasma nedocromil levels were reported from several clinical trials after single or multiple dosing of Tilade 0.5% N.S. to pediatric patients 2-12 years old. Their mean plasma levels ranged from 3.1 ± 1.9 to 8.6 ± 2.3 ng/ml 30-60 min post dosing. The sponsor indicated that 1) there is no accumulation occurred and 2) the above mean plasma levels are similar to those obtained from adults and consistent with those obtained from 2 x 2 mg Tilade aerosol MDI in pediatric patients. The sponsor's statement is seemingly acceptable.

There are no PK/Bio studies conducted for patients with hepatic or renal impairment nor for drug-drug (D-D) interaction. For the assay methods and their validation reports, the sponsor indicated that the reports were submitted and reviewed previously under NDA 19-660. Standard curves were reportedly constructed for each individual study, but they were not provided. Upon the Agency's request, resubmitted were validation reports plus representative standard curves for plasma and urinary samples for one pivotal study. They are found satisfactory. Finally, the results of quality assurance (QA) for the above assay methods are also found satisfactory.

RECOMMENDATION:

NDA 20-750 for Tilade 0.5% Nasal Solution (nedocromil sod.) that was submitted on 09/30/96, the sponsor's responses that were submitted on 05/12/97, 06/02/97, 06/10/97, and 06/23/97, and the draft labeling submitted on 07/25/97 after revision have been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB/DPE II is of the opinion that the human PK/Bio section of this NDA is overall acceptable.

Tien-Mien Chen
06/26/97
Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Dale P. Conner, Pharm.D. DPC 06/26/97
FT initialed by Dale P. Conner, Pharm.D. DPC 8/6/97

cc: NDA 20-750, HFD-570 (Otulana, Gallauresi), HFD-870 (M.L. Chen, D. Conner, T.M. Chen), CDR (B. Murphy).

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Appendix 1:

Appendix 1 contains 10 individual study reports (6 pivotal and 4 supportive) under this NDA.

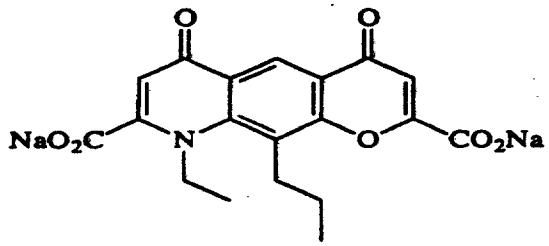
Appendix 2:

Appendix 2 contains additional detailed information such as PI (Sponsor's revised version on 07/25/97), batch size/no. used, etc. It is being retained in DPE II and can be obtained upon request.

I. BACKGROUND:

Tilade (nedocromil sod.) 0.5% N.S. is an isotonic, clear, yellow, sterile solution to be used as an inhaled anti-inflammatory agent. Each ampoule contains 11 mg of nedocromil sod. in 2.2 ml of aqueous solution.

Nedocromil is a pale yellow powder of pyranoquinoline disod. salt with a molecular weight of 415.3. It is soluble in water and its structure is shown below:



Nedocromil sod. inhibits the activation and release of mediators (including histamine, leukotriene C_4, and prostaglandin D_2) in vitro from a variety of inflammatory cell types associated with asthma, but it does not belong to glucocorticoid anti-inflammatory drugs.

II. SUMMARY OF PHARMACOKINETICS, BIOEQUIVALENCE, PHARMACODYNAMICS, ETC.:

Ten new PK studies that were submitted under NDA 20-750 were reviewed. Six studies were considered pivotal as summarized below:

Table 1:

Study No.	Short Title	Study Design	Subj. (M/F)	Age (Range)	Dosing Regimen
CP/HV 268	Comparative PK in Healthy Volunteers for Systemic Bioavailability	Open, Randomized, 3 x 3 Crossover, Single-Dose	12 (6M/6F)	39.0 (27-59)	20 mg Nedocromil N. S. (via **Henley Jet-Fan** nebulizer), 4 mg P. Aerosol MDI, and 0.42 mg IV
CR 2524	Comparative PK in Japanese Male Volunteers	Open, Randomized, 2 x 2 Crossover, Single-Dose	12 (12M)	21.8 (20-23)	10 mg Nedocromil N. S. (via **Millicon** nebulizer) and 4 mg P. Aerosol MDI
CP 8352	Comparative PK in Healthy Volunteers	Open, Randomized, 2 x 2 Crossover, Single-Dose	8 (4M/4F)	38.5 (28-52)	10 mg Nedocromil N. S. (via **Omron** nebulizer) and 4 mg P. Aerosol MDI
CP/HV 322	Comparative PK via different nebulizers with and without 2x dilution of N.S. in Healthy Volunteers	Open, Randomized, 5 x 5 Crossover, Single-Dose	10 (5M/5F)	31.1 (20-44)	10 mg Nedocromil N. S. (via **Henley Fan-Jet, Pulmosonic** w&w/o 2x dilution and **Medix** nebulizer w&w/o 2x dilution)
CR 1068	Response-Drug Concentration Study for EIB[a] in patients	Double-Blind, 5 x 5 Crossover, Single-Dose	11 (11M)	37.2 (17-54)	Placebo and 4 ml of 0.05%, 0.5%, 1% and 2% Nedocromil N. S. (via **Wright** nebulizer)
CR 1340	Duration and Response Study for EIB in patients	Double-Blind, 4 x 4 Crossover, Single-Dose	11 (8M/3F)	31.9 (16-50)	Placebo and 4 ml of 0.05%, 0.25%, and 1% Nedocromil N. S. (via **Wright** nebulizer)

a. Exercise-induced bronchoconstriction (EIB).

1. PHARMACOKINETICS:

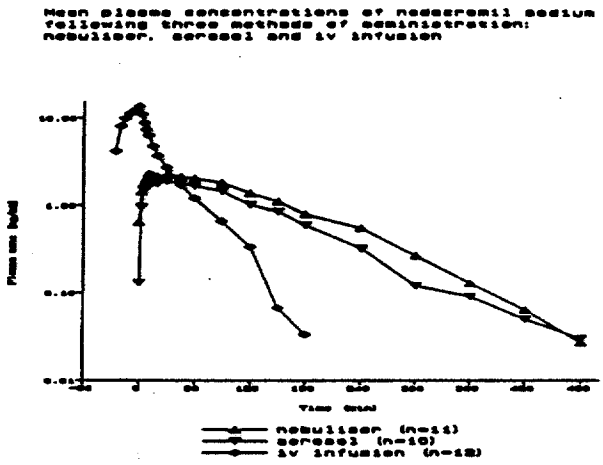
The PK of single-doses of 2 x 0.5% (a nominal dose of 20 mg) of nedocromil N.S. via **Henley Fan-Jet** nebulizer and 2 x 2 mg/actuation of nedocromil pressurized aerosol MDI as compared to an IV infusion in healthy volunteers was investigated in Study No. CP/HV268. The results are summarized below in Table 2 and mean profiles are shown in Figure 1:

Table 2:

Treatment	Nebulizer[a] (n = 11)	Aerosol[b] (n = 10)	IV Infusion (n = 12)
Parameter\Dose	20 mg	4 mg	0.42 mg
C_{max} (ng/ml)	2.6 (1.4)[c]	2.1 (1.0)	13.4 (2.3)
T_{max} (min)	27.5 (19.7)	37.3 (32.0)	30.[d]
AUC_{0-t}[e] (ng-hr/ml)	6.2 (4.3)	4.6 (3.2)	8.9[f] (2.0)
$T_{1/2}$[g] (min)	------	------	31.6 (7.6)
Ae_{0-24}[h] (μg)	206 (121)	162 (97)	212 (54)

a. To-be-marketed formulation of Tilade Nebulizer Solution.
b. Currently marketed Tilade (nedocromil) Inhalation Aerosol MDI.
c. Mean (±SD).
d. Peaked at the end of the 30-min infusion.
e. AUC_{0-t} is for AUC from time zero to the last sampling point of detectable plasma drug level.
f. $AUC_{0-\infty}$.
g. Terminal or β-phase $T_{1/2}$.
h. Amount of drug (μg) excreted in 0-24 hr urine.

Figure 1:



The above results showed that after a 30-min IV infusion of 0.42 (± 0.05) mg nedocromil N.S., 1) plasma nedocromil levels followed a pattern of two-exponential decay with a mean $T_{1/2}$ of 5.3 (±1.8) min for α phase (not shown here) and 31.6 (±7.6) min for β or terminal phase, 2) mean CL was calculated to be 797 ±186 ml/min, and 3) they are consistent with those obtained previously. Mean F_{abs} values for 4 mg nedocromil pressurized aerosol MDI were estimated to be 6 and 8% based on AUC and urinary data, respectively.

Note: The above reported PK data for the nominal dose of 20 mg N.S. could not be quantitatively assured, because the residual volume of inhalation solution was not counted after the end of 5-min inhalation. The above inhalation data set was, therefore, discounted. Please see General Comment No. 4 for details.

A single-dose study No. CR 2524 was conducted in Japan employing **Millicon** nebulizer with 0.5% nedocromil N.S. (1 x 10 mg dose) and nedocromil pressurized aerosol MDI (2 x 2 mg) in 12 healthy male adults. The results showed that **Millicon** gave lower C_{max} and AUC_{0-t} values (2.90 ± 1.1 ng/ml and 5.93 ± 2.56 ng-hr/ml) as compared to those obtained from MDI (5.17 ± 1.88 ng/ml and 13.0 ± 5.7 ng-hr/ml). However, the results of another single-dose study No. CP 8352 (conducted using the same doses of nedocromil N.S. and MDI except a different nebulizer, **Omron**) showed that **Omron** gave higher C_{max} and AUC_{0-t} values (10.4 ± 5.7 ng/ml and 22.9 ± 8.4 ng-hr/ml) as compared to those obtained from MDI (3.6 ± 1.6 ng/ml and 10.2 ± 4.9 ng-hr/ml). The mean T_{max} values for nedocromil using these nebulizer devices, however, were comparable ranging from 22.5 to 24 min and they were also consistent with that (27.5 min) presented in Table 2.

In study CP/HV 322, plasma and urinary PK of a single dose of 0.5% nedocromil (1 x 10 mg) were investigated using **Henley Fan-Jet** (as a reference), **Medix** (with and without 2 x dilution), and **Pulmosonic** (with and without 2 x dilution). The results are summarized below in Table 3:

Table 3:

Devices	Henley Fan-Jet (Reference)	Medix	Medix (with 2x dilution)	Pulmosonic	Pulmosonic (with 2x dilution)
Inhal. Time (min)	5.2 ± 1.2[a]	2.5 ± 1.0	4.2 ± 0.8	4.5 ± 1.3	7.2 ± 1.3
C_{max} (ng/ml)	3.9 ± 1.6	4.5 ± 1.4	8.3 ± 3.7	3.9 ± 1.3	5.9 ± 3.6
T_{max} (min)	45.5 ± 30.3	22.0 ± 14.6	16.5 ± 12.7	28.0 ± 24.3	31.1 ± 21.0
AUC_{0-t}[b] (ng-hr/ml)	10.0 ± 5.3	10.9 ± 5.3	21.5 ± 4.6	8.74 ± 3.59	15.7 ± 9.1
Ae_{0-24} (μg)	196 ± 103	225 ± 98	501 ± 179	269 ± 381	320. ± 261

[a]. Mean ± SD.

[b]. AUC_{0-t} is for AUC from time zero to the last sampling point of detectable plasma drug level.

The above study results demonstrated that 1) without 2 x dilution, **Henley Fan-Jet, Medix,** and **Pulmosonic** nebulizers gave minor differences in mean C_{max}, AUC, and Ae values, but they were not statistically significant, 2) mean T_{max} for **Henley Fan-Jet** is significantly different from those for the other treatments, and 3) a 2 x dilution evidently gave higher mean C_{max}, AUC, and/or Ae values and some of them were statistically significant as compared to the reference.

Consistent results were obtained from a supportive PK study (No. CR 2175/1) for investigating similarly the effects of 2 x dilution (blood samples being monitored up to 2 hr post dosing only). Nevertheless, dilution is not the subject of this NDA seeking approval.

Additional supportive PK studies investigated "handmade" **Omron** nebulizer devices (Study No. CP 8350) or penetration of hypotonic (≈0.3% saline) and hypertonic (≈5% saline) radiolabelled 0.5% nedocromil N.S. into the coronal mid-lung and transverse mid-lung via **Inspiron** nebulizer (Study No. CR 2135/0). They were briefly reviewed. The results obtained from Study No. CR 2135/0 showed that mean penetration index was significantly greater for the hypotonic than the hypertonic N.S. (P=0.0055). The sponsor indicated that a relationship between smaller droplets formed and hypotonicity of the solution is likely. Nevertheless, they were not the subject of this NDA either.

No multiple-dose PK/Bio studies were conducted in healthy volunteers or in target population under this NDA. Single-point plasma nedocromil levels were reported from several clinical trials in pediatric patients. After multiple dosing of Tilade 0.5% N.S., their mean plasma levels were 3.1 ± 1.9 ng/ml 60 min post last dose after a 12-month treatment period and were 4.8 ± 1.1 ng/ml (n=10; 4-10 years old) 40 min post a 2-week QID treatment. Additional mean plasma nedocromil levels reported ranged from 3.3 ± 1.9 to 8.6 ± 2.3 ng/ml 30-50 min post single dosing to pediatric patients of 2-12 years old. The sponsor indicated that 1) there is no accumulation occurred and 2) the above mean plasma levels are similar to those obtained from adults and consistent with those obtained from 2 x 2 mg Tilade aerosol MDI in pediatric patients. The sponsor's conclusion is seemingly acceptable.

2. BIOEQUIVALENCE:

No BE study was conducted, since the to-be-marketed formulation has been tested in the PK/Bio and clinical trials.

3. DOSE PROPORTIONALITY:

In a supportive study No. CP/HV 216, 2 ml of 0.25% (5 mg dose), 0.5% (10 mg), 1% (20 mg), 2% (40 mg), and 4% (80 mg) of nedocromil N.S. were given to 6 healthy volunteers but the plasma levels were only monitored between 0-4 and at 24 hr (not detectable) post dosing. Mean C_{max} (1.3, 2.4, 7.0, 10.6, and 28.3 ng/ml) and extrapolated AUC_{0-24} (2.8, 6.2, 15.4, 32.1, and 67.9 ng-h/ml) values are seemingly proportional to doses. No other dose-proportionality studies were conducted for nedocromil N.S. in healthy or target population.

4. METABOLISM:

The in vivo metabolism of nedocromil had been studied and submitted for review previously under NDA 19-660 (Study No. SE 5989). An IV infusion of ^{14}C nedocromil was given over one hr to two volunteers. It was reviewed and concluded that 1) urinary excretion of radioactivity accounted for 64% of the dose (up to 3 days), 2) 97% of the above excreted radioactivity was collected within 4 hr post dosing, 3) fecal excretion accounted for the rest of 36% up to 6 days, and 4) nedocromil is not metabolized which is consistent with animal data.

The results of previously reviewed in vitro study (No. 5664) showed that 1) around 6% of ^{14}C-nedocromil was associated with packed RBC fraction, 2) f_b was about 89%, and 3) f_b for rabbit, dog, and mice were around 80, 70, and 40%, respectively.

5. POPULATION:

There were no PK/Bio studies conducted in patients with hepatic or renal impairment.

6. GENDER:

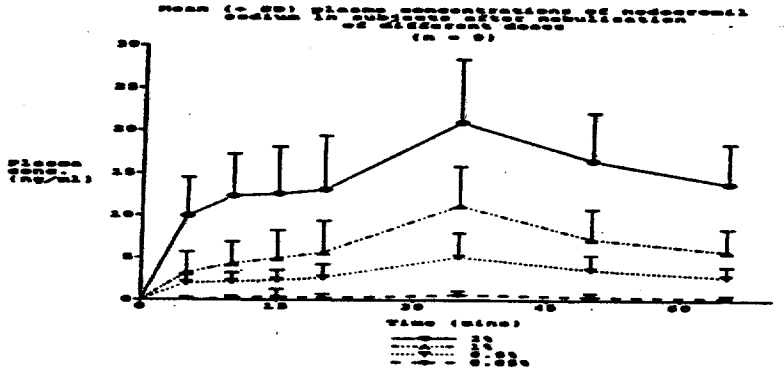
Small numbers of male and female subjects were enrolled in most of the PK/Bio studies. No major gender differences were found.

7. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

Two PK studies (Nos. CR 1068 and CR 1340) were conducted in a small number of patients for EIB (an indication not to be sought for approval of this NDA). In Study No. 1068, 1) 4 ml of 0.05% (2 mg dose), 0.5% (20 mg), 1% (40 mg), or 2% (80 mg) of nedocromil N.S. was given to 11 male patients via Wright nebulizer, 2) plasma nedocromil levels were

monitored up to 65 min post dosing, 3) FEV_1 was monitored at baseline and prior to and during the exercise challenge, and 4) the exercise challenge was initiated 15 min after the 5-min dosing period. Mean plasma nedocromil levels are shown below in Figure 2:

Figure 2:



It was found that plasma nedocromil levels were almost doubled after the challenge of exercise (at around 35 min post dosing; Figure 2). As stated by the sponsor, the above increase was unexpected and no explanation was provided.

Maximum % protection of EIB, calculated as [% maximum fall in FEV_1(control) - % maximum fall in FEV_1 (after treatment)]/ % maximum fall in FEV_1(control) x 100%, at different doses are summarized below in Table 4 and Figure 3:

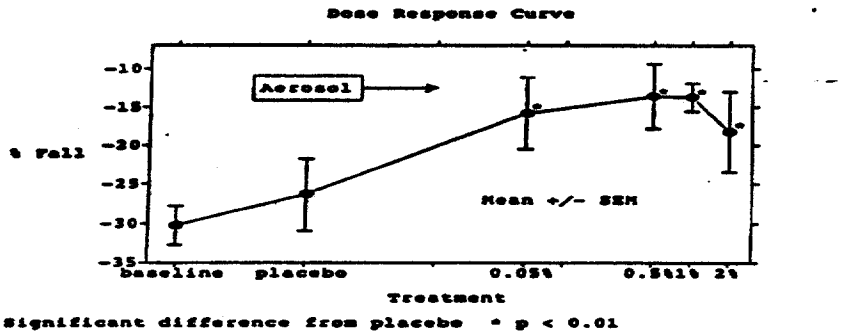
Table 4:

Treatment	Mean (± SD) Maximum Percent Protection
placebo	8.9 ±36.0
2 mg	58.8 ± 26.7
20 mg	65.0 ± 18.9
40 mg	58.8 ± 23.1
80 mg	56.7 ± 27.0

The above results showed that 1) all active treatments gave a more than 55% greater protection compared to control and the differences were statistically significant ($P<0.01$), 2) no differences among the active treatments were found, and 3) their effects were similar to that (62.7%)

after administration of 4 mg Tilade pressurized aerosol MDI during the screening test.

Figure 3:



In another study (No. CR 1340), the duration of action after administration of each of the following single doses, 4 ml of 0.05% (2 mg dose), 0.25% (10 mg), and 1% (40 mg) nedocromil N.S. was investigated in 11 (8M/3F) patients. Three exercise challenges of EIB were performed at 30, 135, and 255 min post dosing. Fifteen min before the 1st challenge and 5 min before the 2nd and 3rd challenges, blood samples were taken. Plasma nedocromil levels were summarized below in Table 5 and their PD effects in Table 6:

Table 5:

	Mean (±SD) Plasma Drug Levels (ng/ml)			
Time\Dose (min)	Placebo	0.05% (2 mg)	0.25% (10 mg)	1% (40 mg)
0	**	*	*	*
15	*	0.2 ± 0.2	1.4 ± 0.7	3.9 ± 1.3
130	*	0.3 ± 0.8	0.7 ± 0.2	2.2 ± 0.5
250	*	0.2 ± 0.5	0.3 ± 0.2	1.1 ± 0.5

Not detectable.

Table 6:

	Mean (± SD) Maximum % Protection for Challenge			
Challenge\Dose	Placebo	0.05% (2 mg)	0.25% (10 mg)	1% (40 mg)
After 1st exercise	7.4 ±15.6	61.6 ±27.4	71.0 ± 14.1	73.8 ±17.7
After 2nd exercise	-1.6 ±23.7	44.0 ±35.5	67.7 ± 19.9	65.6 ±22.4
After 3rd exercise	-11.0 ±22.2	38.4 ±28.4	54.9 ±28.1	36.1 ± 30.

The above results demonstrated that 1) all active treatments gave a good protective effect at all times of challenges, 2) the differences among the doses or the challenges after active treatments were not significant, and 3) there was a tendency of decrease in protective effect with time and/or repeated exercises.

8. DRUG-DRUG INTERACTION:

There were no D-D interaction PK studies conducted to address this issue.

9. FORMULATIONS, DOSAGE, AND DRUG ADMINISTRATION:

The to-be-marketed formulation 0.5% (10 mg in a 2-ml ampoule) was used in most of the PK/Bio studies except for the last two pivotal studies reviewed in which nedocromil N.S. was diluted from higher concentrations with normal saline at the study site(s). Its formulation is 5 g nedocromil and 7.9 g NaCL then qs. to 1 liter with water for injection USP. The pH of the solution is adjusted by HCL between 4 and 5.5.

10. ASSAY METHODOLOGY:

III. - GENERAL COMMENTS: (No. 5 needs to be sent to the sponsor)

1. Several single-dose PK studies were conducted in healthy volunteers in order to compare the PK of nedocromil administered via different nebulizer devices. In study No. CP/HV 322, **Henley Fan-Jet, Medix**, and **Pulmosonic** nebulizers demonstrated comparable mean C_{max} and AUC values when the Tilade 0.5% N.S. used was not diluted. In two other PK studies, different type of nebulizer device was employed in each study for Tilade 0.5% N.S. (Tilade pressurized aerosol MDI was used as a reference) and controversial PK results were obtained. Therefore, it is to bring to the reviewing medical officer's attention that large variation in nedocromil C_{max} or AUC values existed among studies which could be due to the variability in delivery by different nebulizer devices.

2. Study in EIB showed that the mean C_{max} in patients was almost doubled after exercise. No explanation was provided by the sponsor. This reviewer is of the opinion that it could be due to an increase of absorption of nedocromil from the lungs after exercise as a result of an increase in cardiac output to the lungs.

3. The age range which is currently being sought for approval of Tilade 0.5% nebulizer solution is 2 years and older, however, no single or multiple-dose PK/Bio studies of nedocromil were conducted in younger patients down to age 2 to support the above claim. Since 1) single-point plasma nedocromil levels were obtained from several clinical trials and 2) the results showed that no accumulation of nedocromil in vivo occurred, and 3) their mean plasma levels, 3.1-8.6 ng/ml, are consistent with those obtained from adults and from Tilade aerosol MDI in pediatric patients, no additional single- and/or multiple-dose PK/Bio studies need to be carried out to fulfill the above requirement.

4. Interstudy comparison was performed for Study No. CP/HV 268 and CP/HV 322 which used the same nebulizer device, **Henley Fan-Jet**, and flow rate (3L/min) and similar assay methods except difference doses (2x10 mg/2 ml in CP/HV 268 and 1x10 mg/2 ml in CP/HV 322). The results showed that Study No. CP/HV 268 had lower mean C_{max} and AUC values than Study No. CP/HV 322.

The above discrepancies were discussed with the sponsor (Dr. Steven Miller of RPR) in a telecon on 06/20/97. The sponsor indicated that due to the fact that the residual volume of a nominal dose of 20 mg N.S. in the device was not counted after the end of a 5-min inhalation, no quantitative PK data could be obtained from the "actual dose" inhaled, therefore, the above data set was discounted.

5. It is recommended that complete assay results be submitted to each individual study which should include standard curves, the lowest limit of quantitation, accuracy, and intraday and interday precisions, intraday and interday precisions for quality control samples, etc. For general information on assay validation, please see Pharmaceutical Research 9:588-592, 1992 for details.

IV. LABELING COMMENTS: (Need to be sent to the sponsor)

1. Under *Absorption* of **Pharmacokinetics** subsection, it is stated " **Tilade** Nebulizer Solution is administered locally to lungs by inhalation. The mechanism of action of nedocromil sodium is believed to be due to topical application to the lung and .....".

   It is not clear whether a topical effect study has been conducted. If "yes", it is recommended that the reference study be cited and the following Agency's version of **Pharmacokinetics** subsection be incorporated. If "No", the above statement should be removed.

2. The Agency's version of Pharmacokinetics subsection:

Pharmacokinetics: The mechanism of action of nedocromil sodium is believed to be due to topical application to the lungs and no direct relationship between plasma concentration and effect is observed.

Absorption: **Tilade** Nebulizer Solution is administered locally to the lungs by inhalation. The bioavailability of inhaled nedocromil sodium is estimated to be low due to the small amount of drug that reaches the lungs. The larger portion of an inhaled dose deposits in the mouth and is swallowed. The absolute bioavailability of nedocromil sodium 0.5% nebulizer solution, however, was not determined. The bioavailability of nedocromil sodium from the GI tract is low (~ 2%) and that for nedocromil sodium inhaled via MDI (2 x 2 mg) is similarly low (8% for single and 17% for multiple doses). The slight increase in bioavailability following multiple MDI dosing is attributed to the prolonged GI absorption of the swallowed drug.

Comparable mean peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values were observed within a study that compared a compressed air nebulizer, Henley Fan-Jet, with two ultrasonic nebulizers, Medix and Pulmosonic. However, interstudy

comparisons for other studies showed that there were variations in pulmonary delivery between different nebulizers.

Distribution: Nedocromil is reversibly bound to plasma proteins (up to 89%).

Metabolism: Nedocromil is not metabolized to any extent in humans.

Elimination: Once absorbed, nedocromil is rapidly eliminated from the plasma. The mean clearance of nedocromil after an intravenous dose is approximately 800 ml/min with a mean terminal half-life ($T_{1/2}$) of 32 minutes. Excretion occurs as unchanged compound, mainly in urine (64% to 80%) and also in feces (20 to 36%). No evidence of accumulation of nedocromil has been observed with multiple dosing of nedocromil nebulizer solution in clinical trials.

Special populations:
Geriatrics: A study to assess the effect of age on the pharmacokinetics of nedocromil has not been conducted.

Pediatrics: The pharmacokinetics of nedocromil in pediatrics has not been studied. In clinical trials, pulmonary delivery of 0.5% nebulizer solution in children appears to be similar to that observed in adults. Plasma concentrations in children (0.7 to 8.6 ng/mL) measured at the predicted time to C_{max} (T_{max}; 30 to 60 minutes) were similar to those (2 to 7 ng/mL) obtained for adults when administered under similar nebulizing conditions and volume fills. Plasma concentrations measured after two weeks of treatment at a QID dosing regimen with nedocromil sodium 0.5% nebulizer solution in children indicated a similar exposure profile between multiple and single doses.

Gender and race: The effect of gender and race on the pharmacokinetics of nedocromil has not been studied.

Renal Insufficiency: No specific pharmacokinetic studies have been conducted in renal impaired subjects.

Hepatic insufficiency: No specific pharmacokinetic studies have been conducted in subjects with hepatic failure.

Drug-drug Interactions: Specific pharmacokinetic studies have not been conducted to investigate drug-drug interactions.

3. In the paragraph of Drug Interactions under the Precautions subsection, the first sentence should be modified as follows:

   In clinical trials, **Tilade** Nebulizer Solution has been used concomitantly with other anti-asthma therapies including inhaled and oral bronchodilators and inhaled corticosteroids.

NDA 20-750 (Tilade 0.5% Nebulizer Solution; Nedocromil Sod.)

Appendix 1:

Individual Study Reports

Study No. CP/HV 268 (Volume 1.6)

Title: "Comparative Plasma Concentrations and Urinary Excretion of Nedocromil Sodium Administered by Nebulizer, Pressurized Aerosol, and IV infusion in Healthy Volunteers"

Investigator and Study Site:

The study was conducted by

Objective:

To determine the F_{abs} of 0.5% nedocromil sodium solution administered by nebulizer and pressurized aerosol compared to IV dosing in healthy volunteers.

Study Design:

This was a randomized, Latin-square, 3 x 3 crossover, single-dose study with a washout period of at least 7 days.

Population:

Twelve (6M + 6F) healthy subjects completed the study and their mean (± SD) age, BW, and height are 39.0 (± 10.0) years old, 69.9 (± 8.9) kg, and 172 (± 12) cm, respectively.

Formulation, Dosage, and Administration:

To-be-marketed formulation of Tilade nebulizer solution, currently approved Tilade pressurized aerosol, and isotonic saline containing 25 μg/ml for IV infusion were used.

On the treatment day, the subjects arrived at the clinic after an overnight fast. A standard breakfast (biscuits and orange juice) was served at the clinic 0.5 hr after start of a treatment and the subjects abstained from food for 4 hr post dosing.

The following doses were given: a mean (±SD) dose of 0.42 ± 0.05 mg nedocromil was given by IV infusion (0.2 μg/kg/min) within 30 min, 4 ml of 0.5 % aqueous solution of nedocromil (10 mg in 2 ml) was nebulized from a Henley Fan-Jet at a flow rate of 3 liters/min for 5 min, and 2 x 2 mg/actuation of Tilade aerosol.

Sample Collection:

Venous blood (5 ml each) was withdrawn immediately before dosing and at 2.5, 5, 7.5, 10, 20, 30, 45, 60 min and 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hr post nasal administration. For IV treatment phase, blood was taken immediately before dosing and at 5, 10, 15, 20, and 25 min during IV infusion and 0, 2.5, 5, 7.5, 10, 20, 30, 45, 60 min and 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hr post 30-min IV infusion. Blood samples were immediately centrifuged. Plasma was harvested and stored frozen at -20°C until analysis.

Urine samples were collected between 0-6, 6-24, 24-48, and 48-72 hr post each dosing and an aliquot of urine from each interval was immediately frozen and stored at -20°C until assayed.

Assays:

Data Analyses:

Non-compartmental methods were used for calculating the PK parameters of nedocromil and descriptive statistics were used.

Results:

Individual nedocromil plasma levels were spot checked and they were found acceptable. However, due to the fact that the residual volume of the 20-mg inhalation solution was not counted after the end of 5-min inhalation, its data set was, therefore, discounted.

APPEARS THIS WAY
ON ORIGINAL

Study No. CR 2524 (Volume 1.7)

Title: "A Comparative Study of the PK of Nedocromil Sod. Administered by Pressurized Aerosol or as a Nebulized Solution in Healthy Volunteers"

Investigator and Study Site:

The study was conducted by

Objective:

To 1) evaluate the safety of nedocromil inhalation solution and 2) compare its PK after single-dose administration by inhalation of nebulized solution and spray-type aerosol in healthy male adult volunteers.

Study Design:

This was an open, randomized, Latin-square design, 2 x 2 crossover, single-dose study with a washout period of 7 days.

Population:

Twelve healthy Japanese male adults completed the study and their mean (± SD) age, BW, and height are 21.8 (± 0.9) years old, 59.7 (± 6.3) kg, and 170. (± 4.0) cm, respectively.

Formulation, Dosage, and Administration:

To-be-marketed formulation of Tilade nebulizer solution and currently approved Tilade pressurize aerosol were used. For the formulation, batch no./size and date/site of manufacture, please see Appendix 2 for details.

On the treatment day, subjects received either one ampoule (10 mg in 2 ml) of nebulized solution for 5 min using an electronic nebulizer Millicon-N through facemask or an aerosol (2 x 2 mg/spray) after an overnight fasting. The subject's mouth was rinsed 3 times with 100 ml of water to remove the drug remaining in the oral cavity. To maintain the urine volume, the subjects drank 200 ml of water 1 hr predosing and 2 hr post dosing. Lunch and dinner were given at 4 and 10.5 hr post dosing.

Sample Collection:

Venous blood (10 ml each) was withdrawn immediately before dosing and at 5, 10, 15, 30, 45 min and 1, 2, 4, 6, and 8 hr post dosing (the time of completion of 5-min inhalation is regarded as time zero). Blood samples were immediately centrifuged at 4°C, 300 rpm for 10 min. Plasma was harvested and two aliquots were stored frozen at -20°C until analysis.

Urine samples were collected before dosing and between 0-2, 2-4, 4-8, 8-12, and 12-24 hr post dosing. Urine samples are stored at 4°C before processing and then two 10-ml samples were collected and stored at -20°C until analysis

Assays:

Data Analyses:

Non-compartmental methods were used for calculating the PK parameters of nedocromil and descriptive statistics were used.

Results:

Individual nedocromil plasma and urinary levels were spot checked and they were found acceptable. For study results, please see PK summary of this bioreview for details.

APPEARS THIS WAY
ON ORIGINAL

Study No. CP 8352 (Volume 1.8)

Title: " A PK Study Using Nedocromil Sod. Nebulizer Solution To Investigate the Performance of the Omron Nebulizer Device"

Investigator and Study Site:

The study was conducted by

Objective:

To compare the PK profiles of nedocromil sod. after its administration by Omron device and by an MDI.

Study Design:

This was an open, randomized, 2 x 2 crossover single-dose study with a washout period of 7 days.

Population:

Eight healthy adults (4M+4F) completed the study and their mean (± SD) age, BW, and height are 38.5 (± 7.9) years old, 72.8 (± 11.1) kg, and 168 (± 13) cm, respectively.

Formulation, Dosage, and Administration:

To-be-marketed formulation of Tilade nebulizer solution and currently approved Tilade pressurize aerosol were used. For the formulation, batch no./size and date/site of manufacture, please see Appendix 2 for details.

On the treatment day, subjects received either one ampoule (10 mg in 2 ml) of nebulized solution until finished using Omron nebulizer devices (Nos. 24 and 36) with a facemask or an aerosol (2 x 2 mg/spray) after an overnight fasting. Two, 3, and 4 hr post dosing, 150 ml orange juice, 150 ml water, and a standard lunch with 150 ml water and decaffeinated coffee were given, respectively.

Note: It was not clear as to whether the subject's mouth was rinsed to remove the drug remaining in the oral cavity.

Sample Collection:

Venous blood (5 ml each) was withdrawn immediately before dosing and at 5, 10, 15, 20, 30, 45, 60 min and 1.5, 2, 2.5, 3, 4, 5, and 6 hr post nasal administration. Blood samples were immediately centrifuged. Plasma was harvested and stored frozen at -20°C until analysis.

Assays:

Data Analyses:

Non-compartmental methods were used for calculating the PK parameters of nedocromil. However, no formal statistical testing was carried out.

Results:

Individual nedocromil plasma levels were spot checked and they were found acceptable. For study results, please see PK summary of this bioreview for details.

APPEARS THIS WAY
ON ORIGINAL

Study No. CP/HV 322 (Volume 1.8)

Title: "Comparative Plasma Concentrations and Urinary Excretion of Nedocromil Sod. Administered by Medix and Pulmosonic Nebulizers, With and Without Dilution With Saline and Henley Fan-Jet as Reference, Using An Aqueous Solution in Healthy Volunteers"

Investigator and Study Site:

The study was conducted by

Objective:

To obtain plasma and urinary PK data for nedocromil from two new nebulizers and to compare the results with previous PK data obtained from other nebulizer.

Study Design:

This was an open, randomized, 5-way crossover single-dose study with a washout period of 3 days.

Population:

Ten healthy adults (5M + 5F) completed the study and their mean (± SD) age, BW, and height are 31.1 (± 9.9) years old, 67.4 (± 12.3) kg, and 169 (± 12) cm, respectively.

Formulation, Dosage, and Administration:

To-be-marketed formulation of Tilade nebulizer solution and currently approved Tilade pressurize aerosol were used. For the formulation, batch no./size and date/site of manufacture, please see Appendix 2 for details.

On the study day, subjects received one of the following treatments after an overnight fasting:

1. Henley Fan-Jet (10 mg in 2 ml as reference): flow rate 3 l/min with the close mouth technique and a nose-clip.
2. Pulmosonic with no dilution with saline (10 mg in 2 ml): flow rate ? L/min with or without nose-clip.
3. Pulmosonic with dilution with saline (10 mg in 4 ml): the same above.

4. Medix with no dilution with saline (10 mg in 2 ml): the same above.
5. Medix with dilution with saline (10 mg in 4 ml): the same above.

Two, 3, 4, and 6 hr post dosing, 150 ml orange juice, 150 ml water, standard lunch with 150 ml water and 150 ml decaffeinated coffee, and 150 ml water were given, respectively.

Note: It was not clear as to whether the subject's mouth was rinsed to remove the drug remaining in the oral cavity.

Sample Collection:

Venous blood (5 ml each) was withdrawn immediately before dosing and at 5, 10, 15, 20, 30, 45, 60 min and 1.5, 2, 2.5, 3, 4, 5, 6, and 24 hr post nasal administration. Blood samples were immediately centrifuged. Plasma was harvested and stored frozen at -20°C until analysis.

Urine samples were collected immediately before dosing and between 0-6 and 6-24 hr post dosing. Urine samples were stored frozen at -20°C until analysis.

Assays:

Data Analyses:

Non-compartmental methods were used for calculating the PK parameters of nedocromil and descriptive statistics were used.

Results:

Individual nedocromil plasma and urinary levels were spot checked and they were acceptable. For the PK parameter, mean $AUC_{t-\infty}$ value, calculated for each treatment phase (without dilution), it represented around 1/3 of the mean $AUC_{0-\infty}$ obtained which is not really ideal. Therefore, only the mean AUC_{0-t} values were reported. For study results, please see PK summary of this bioreview for details.

Study No. CR 1068 (Volume 1.9)

Title: "The Effect of Nedocromil Sod. Given by Nebulizer on Exercise-Induced Bronchoconstriction-Dose/Plasma Concentration/Response"

Investigator and Study Site:

The study was conducted by

Objective:

To compare the protective effects of various doses of nedocromil given by Wright nebulizer and to relate the effects to plasma concentration in asthmatic patients.

Study Design:

This was a double-blind, 5 x 5 crossover, single-dose study with a washout period of 3-4 days.

Population:

Eleven male asthmatic patients completed the study and their mean (± SD) age, BW, and height are 37.2 (± 11.9) years old, 76.2 (± 9.2) kg, and 174 (± 6) cm, respectively.

Formulation, Dosage, and Administration:

To-be-marketed (0.5%), not to-be-marketed (0.05, 1, and 2%) formulations of Tilade nebulizer solution, and placebo were used. For the formulation, batch no./size and date/site of manufacture, please see Appendix 2 for details.

One exercise test was performed at the similar times of day for each of the 5 occasions. The following single doses were given 20 min prior to exercises, placebo, 4 ml x 0.05% (2 mg), 4 ml x 0.5% (20 mg), 4 ml x 1% (40 mg), and 4 ml x 2% (80 mg). Wright nebulizer at a flow rate of 9 l/min x 5 min using a facemask were employed.

Sample Collection:

Venous blood (5 ml each) was withdrawn immediately before dosing and at 5 (the end of nebulization), 10, 15, 20 (immediately before exercise), 30, 35, 50, and 65 min post dosing. Blood samples were immediately centrifuged. Plasma was harvested and stored frozen at -20°C until analysis.

Assays:

Data Analyses:

Non-compartmental methods were used for calculating the PK parameters of nedocromil. However, no formal statistical testing was carried out.

Results:

Individual nedocromil plasma levels were spot checked and they were found acceptable. For study results, please see PK summary of this bioreview for details.

Study No. CR 1340 (Volume 1.9)

Title: "Duration of Action and Plasma Concentration of Doses of 0.05, 0.25, and 1% Nedocromil Sod. Delivered by Nebulizer In Exercise-Induced-Asthma"

Investigator and Study Site:

The study was conducted by

Objective:

To compare the protective effects of three doses of nedocromil given by Wright nebulizer to EIB patients and to relate the effects to plasma concentration in these patients.

Study Design:

This was a double-blind, 4x4 crossover, single-dose study with 3 challenges per each treatment leg and a washout period of 3-4 days for each treatment using Wright nebulizer.

Population:

Eleven patients (8M + 3F) were enrolled and 10 completed the study. Their mean (± SD) age, BW, and height are 31.9 (± 12.0) years old, 73.9 (± 15.4) kg, and 172 (± 9) cm, respectively.

Formulation, Dosage, and Administration:

To-be-marketed (0.5%), not to-be-marketed (0.05, 0.25%, and 1%) formulations of Tilade nebulizer solution, and placebo were used. For the formulation, batch no./size and date/site of manufacture, please see Appendix 2 for details.

Three exercise tests were performed in each of the four occasions, at the similar times of day for each occasion. The following single doses were given 15 min prior to exercises, placebo, 4 ml x 0.05% (2 mg), 4 ml x 0.25% (10 mg), and 4 ml x 1% (40 mg). Wright nebulizer at a flow rate of 9 l/min x 5 min using a facemask were employed.

Sample Collection:

Venous blood (5 ml each) was withdrawn immediately before dosing and at 0.25 hr prior to each of the 3 challenges (at 0.25, 2.25, 4.25 hr) per each treatment occasion. Blood samples were immediately centrifuged. Plasma was harvested and stored frozen at -20°C until analysis.

Assays:

Data Analyses:

Non-compartmental methods were used for calculating the PK parameters of nedocromil. However, no formal statistical testing was carried out.

Results:

Individual nedocromil plasma levels were spot checked and they were found acceptable.