Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-009 SUBMISSION DATE: 3/31/99, 4/19/99 4/30/99

NDA TYPE: 3P

PRODUCT: ABREVIA™
(Nedocromil sodium ophthalmic solution, 2%)

SPONSOR: Allergan Inc.
Irvine, CA

REVIEWER: Veneeta Tandon, Ph.D.

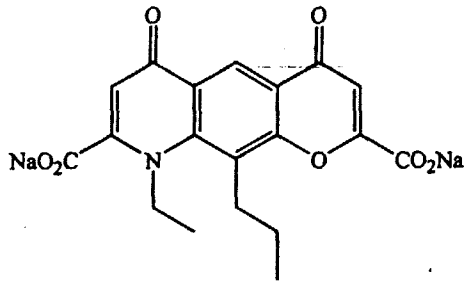
Review of a NDA

I. BACKGROUND

Indication: Nedocromil sodium ophthalmic 2% solution is indicated for the prevention and treatment of allergic conjunctivitis

Pharmacological Class: Mast cell stabilizer and anti-inflammatory agent

Dose and administration: The recommended dosage for adults and children 2 years and older is one or two drops in each eye twice a day until pollen season is over



Allergic conjunctivitis and vernal conjunctivitis are allergic diseases caused by antigens, such as various pollens, mites and house dust. The pathophysiological response in allergic conjunctivitis is initiated by the release of mediators from the inflammatory cells and the mast cells. Generally these diseases are treated by symptomatic therapy with corticosteroids. Lately disodium chromoglycate ophthalmic solution has been widely used as an antiallergenic ophthalmic solution, which inhibits release of chemical mediators from mast cells.

Discipline /S/

Nedocromil sodium, a mast cell stabilizer and anti-inflammatory agent is the disodium salt of a pyranoquinoline acid and has been shown in vitro to inhibit mediator release from at least two types of mast cells. The mast cell stabilizers are used mostly as a prevention, rather than treatment of allergic conjunctivitis.

In vitro studies on cells obtained by bronchoalveolar lavage from antigen-sensitized macaque monkeys found to be rich in mucosal mast cells, show that nedocromil sodium clearly inhibits the release of histamine and inflammatory mediators, leukotriene C_4 and prostaglandin D_2. *In vitro* studies with human bronchoalveolar cells showed that nedocromil sodium inhibits histamine release from a population of mast cells having been defined as belonging to the mucosal sub type and betaglucuronidase release from macrophages.

In addition, it inhibits the activation of, and mediator release from, a variety of other inflammatory cell types associated with allergic conjunctivitis including eosinophils, macrophages, monocytes and platelets. Nedocromil sodium has no intrinsic vasoconstrictor or antihistaminic activity.

Foreign Marketing History: 2% ophthalmic solution of nedocromil sodium has been marketed in many countries in Europe since 1993, in Canada since 1997 and in Australia since 1996. Also used as an inhalant asthma therapy (TILADE™-Rhone-Poulenc Rorer) in U.S., Canada, Europe and Middle East. The recommended dosage for adults and pediatric patients 6 years of age and older is two inhalations four times daily at regular intervals, which provided a dose of 14 mg per day.

II. RECOMMENDATION

The sponsor has demonstrated low systemic exposure (less than 4% of the dose) of nedocromil sodium after topical administration of 2% nedocromil sodium ophthalmic solution. The reviewer recommends approval of the application from the pharmacokinetic standpoint. Labeling changes at the end of this review should be incorporated in the label.

Table of Contents

III. FORMULATION

Ingredient	Quantity (g/kg)	Function
Nedocromil sodium	20	
Benzalkonium chloride, 50% w/w		
Edetate sodium		
Sodium chloride		
Purified water		

This to-be-marketed formulation was the formulation that was used in the bioavailability studies. The lot numbers used for Study CP/HV 198 and CP/HV 219 were 1708P and P2420 respectively.

V. PHARMACOKINETIC STUDIES

The sponsor has conducted two topical bioavailability studies to support this application. For other pharmacokinetic characteristics of nedocromil sodium, reference has been made to NDA 19-660 (TILADE inhaler) and NDA 19-995 (TILARIN nasal solution), where the pharmacokinetics of nedocromil sodium has been studied extensively by intravenous, oral, inhalation and intranasal administrations. These NDAs have been reviewed

thoroughly by Dr. Raman Baweja and Dr. Dennis Bashaw. Hence, the other pharmacokinetic characteristics of the drug have not been summarized here. Nedocromil sodium in not metabolized and the drug is eliminated primarily unchanged in the urine (70%) and feces (30%).

***Study SD 4880/3, CP/HV 198:** A study of acceptability, tolerability and urinary excretion of an aqueous solution of nedocromil 0.5%, 1%, 2% and 4% applied to the healthy human eye.*

Study Design

The study was a randomized double-blind study with 4 separate study days, 3 or 4 days apart in 6 subjects (3M and 3F, age 31-36 years, weight 53-83 kg). One drop of placebo (saline control) was placed in one eye and one drop (0.04 mL) of nedocromil sodium in the other eye, the nedocromil being administered in increasing concentration of 0.5%, 1%, 2% and 4% on each separate study day. The corresponding total doses of nedocromil sodium was 0.2, 0.4, 0.8 and 1.6 mg. Urine was collected for nedocromil assay for 6 hours after dose and volume measured. Subjects were to be on no regular concomitant mediation. The subject demographics and volumes of urine collected are attached in the Appendix on page 13.

Results

Since plasma levels of nedocromil sodium would not be reliably quantifiable after ophthalmic administration, the sponsor has calculated the absorption from urinary excretion data.

Mean urinary excretion of nedocromil sodium was proportional to the dose as seen in the following table.

Subject Number	Urinary excretion in µg after treatment with			
	0.5%	1%	2%	4%
12				
31				
73				
78				
111				
121				
Mean	3.8	7.4	14.2	35.0
SEM	0.4	2.1	3.5	11.3

The urinary excretion expressed as percent of dose is shown the following table.

Subject Number	Urinary excretion (% of dose) after treatment with			
	0.5%	1%	2%	4%
12 31 73 78 111 121				
Mean SEM	1.9 0.2	1.9 0.5	1.8 0.4	2.2 0.7

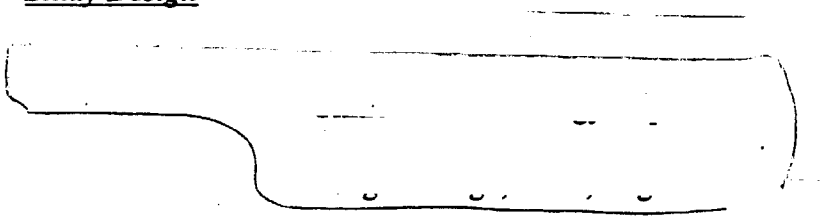
Individual urinary data showed some inter and intra-subject variability. Based on urinary excretion from a previous studies[1,2] following intravenous administration it is known that approximately 70% of the dose is excreted in the urine, Using this figure the urinary excretion from this study corresponds to an absorption of approximately 2.8% of the dose. Since clearance of liquid from the eye involves drainage into the nose, the major part of this absorption is likely is likely to occur in the nasal cavity. The bar diagrams showing the urinary excretion are attached in the Appendix on pages 14-15.

Conclusions

This study provided a preliminary estimate of the absorption of nedocromil sodium following instillation of various doses to the eye. A mean of approximately 2% was excreted in the urine, which corresponded to an estimated absorption of 2.8% of the dose.

Study SD 10087/3, CP/HV 219: *A study of acceptability, tolerability and urinary excretion of an aqueous solution of nedocromil 1% and 2% applied to the healthy human eye.*

Study Design



This was a double-blind group comparative study in 12 subjects (6M and 6F), with half the subjects receiving 1% nedocromil sodium to one eye and placebo to the other eye and the other half receiving 2% nedocromil sodium to one eye and placebo to the other eye for a period of 7 days. The drops were administered 4 times daily, one drop (0.04 mL) to

[1] SE 5982: Human volunteers tolerability and pharmacokinetic study after infusion of [redacted]59002KP.
[2] SE 6135/1: the pharmacokinetics of [redacted]59002KP in healthy volunteers after intravenous and oral administration.

each eye. The total dose of nedocromil sodium per drop corresponded to 0.4 or 0.8 mg per drop, respectively for the 1% and 2% dose respectively and the nominal daily doses were 1.6 and 3.2 mg. Two 24-hour urine collections were done to assess urinary excretion of nedocromil. The subject demographics are attached in the Appendix on page 16.

Study Results

The mean urinary excretion of nedocromil sodium following multiple dosing with 1% solution to the eye is shown in the following table.

Subject Number	Amount excreted (µg) on		% of daily dose excreted on	
	Day 1	Day 7	Day 1	Day 7
21 27 61 76 95 144				
Mean	36	49	2.3	3.1
SEM	4	13	0.3	0.8

The mean urinary excretion of nedocromil sodium following multiple dosing with 2% solution to the eye is shown in the following table. The individual urinary concentrations for the 1% and 2% doses are attached in the Appendix on page 17.

Subject Number	Amount excreted (µg) on		% of daily dose excreted on	
	Day 1	Day 7	Day 1	Day 7
28 56 99 105 129 141				
Mean	65	86	2.1	2.7
SEM	12	25	0.4	0.8

Although the table shows that the mean excretion on the 7th day of dosing was higher (mean carryover of 0.8% of the daily dose) than the first day of dosing, but the difference was not statistically significant ($p > 0.05$). This increase in bioavailability following multiple doses is thought to be due to prolonged GI absorption as also seen with intranasal and inhalation routes. The mean excretion appears to be proportional to the dose. Based on the urinary excretion following intravenous administration from previous studies [1,2], the urinary excretion after ophthalmic administration corresponds to absorption of approximately 3.6% of the dose. This amount absorbed is approximately half of that

after intranasal administration, [redacted] Low systemic bioavailability was seen with intranasal, inhalation as well as oral administration and is consistent with the polar nature of the drug.

Conclusions

Following multiple dose administration of 1% and 2% solutions of nedocromil sodium to the eye, approximately 2.7% of the daily dose was eliminated in the urine corresponding to a total absorption of approximately 3.6%.

V. OVERALL CONCLUSIONS

- The systemic bioavailability of nedocromil sodium 2% ophthalmic solution is low. The absorption is approximately 2.8% after single dose and approximately 3.6% after multiple doses.
- No substantial evidence of accumulation was observed after repeated ocular administration.

V. COMMENT

A subection under the 'Clinical Pharmacology' section named 'Pharmacokinetics and Bioavailability' should be added before the last paragraph in that section.

/S/ 8/12/99

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CC: NDA 21-009 (orig)
HFD-550/Div File
HFD-550/CSO/Gorski
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

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[3] M.G.Neale, Br.J.Clin.Pharmac,1987, 24, 493-501

APPENDIX
NDA 21-009

ANALYTICAL VALIDATION

Table 3: Assay responses obtained by the analyses, as five-fold dilutions, of blank urine samples from six donors expressed as the equivalent concentrations of [redacted]59002KP

Urine donor number	Equivalent concentrations of [redacted]59002KP, ng cm^{-3}	
	Blank early morning-voided urine samples	Blank 24 hour collection urine samples
1 2 3 4 5 6	[redacted]	[redacted]
Mean ± standard deviation	0.77 ± 0.38	0.81 ± 0.31
Overall mean ± standard deviation	0.79 ± 0.33	

Table 4: The effect of differing concentrations of urine, in the dilution of urine analysed, on the accuracy of the method for the determination of added concentrations of FPL 59002KP (10, 100 and 1000 ng cm^{-3}) in undiluted urine samples

Urine donor number	Mean accuracy, %		
	Concentration of urine in dilution of urine sample analysed, %, by volume		
	20	2	0.2
	Concentration of FPL 59002KP in urine, ng cm^{-3}, n = 4		
	10	100	1000
	Dilution of urine sample analysed		
	5-fold	50-fold	500-fold
1			
2			
3			
4			
5			
6			
Mean ± standard deviation	103.3 ± 4.1	99.2 ± 10.7	102.5 ± 5.3

Table 5: Intraday precision of the method of three concentrations of [redacted]59002KP (10, 100 and 1000 ng cm^{-3}) added to undiluted urine samples from six donors

Donor number	Coefficient of variation, % (n = 4)		
	Concentration of FPL 59002KP in undiluted urine sample, ng cm^{-3}		
	10	100	1000
1	[redacted]	[redacted]	[redacted]
2			
3			
4			
5			
6			
Mean ± standard deviation	6.2 ± 4.9	5.07 ± 2.42	7.5 ± 4.1

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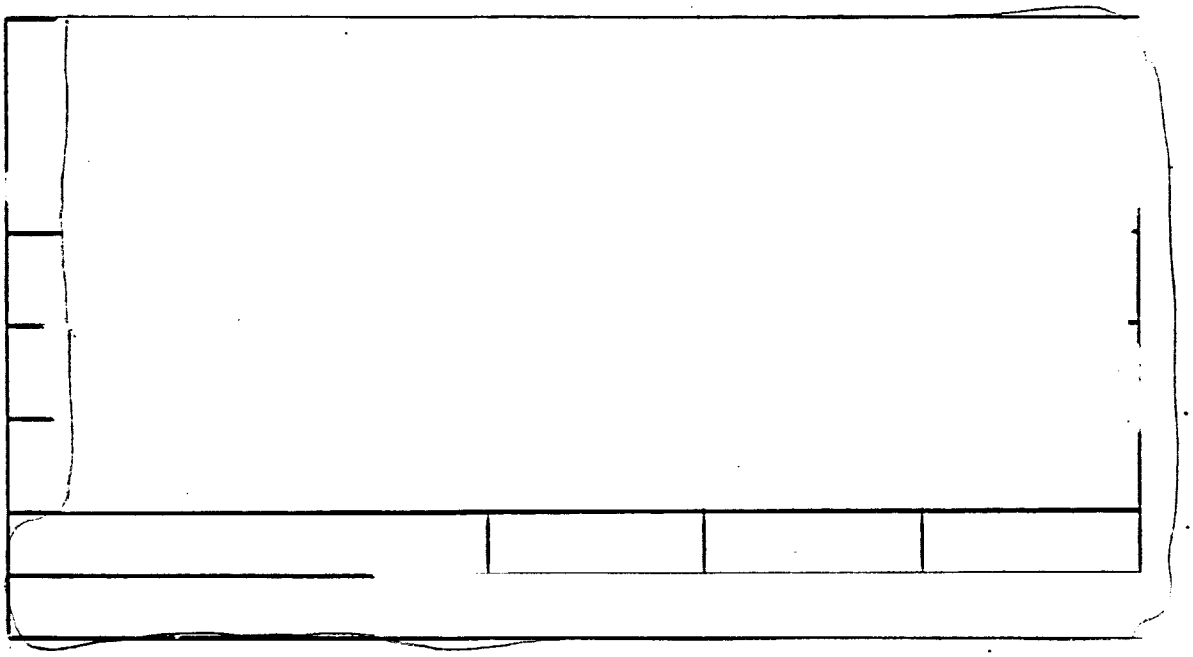
Table 2: Quality control data for the determination of [redacted]59002KP in the urine samples



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STUDY SD 4880/3, CP/HV 198

Table 1

Details of subjects

Subject number	Age (years)	Weight (kg)	Sex M/F
	33	59	M
	31	55	F
	31	63	M
	38	72	M
	37	53	F
	34	83	F

Table 2

Volumes of urine collected

Subject number	Urine volume (ml) after treatment with			
	0.5%	1%	2%	4%
12				
31				
73				
78				
111				
121				

Figure 1 Urinary excretion of pedocromil sodium in volunteers after administration of different doses to the eye.

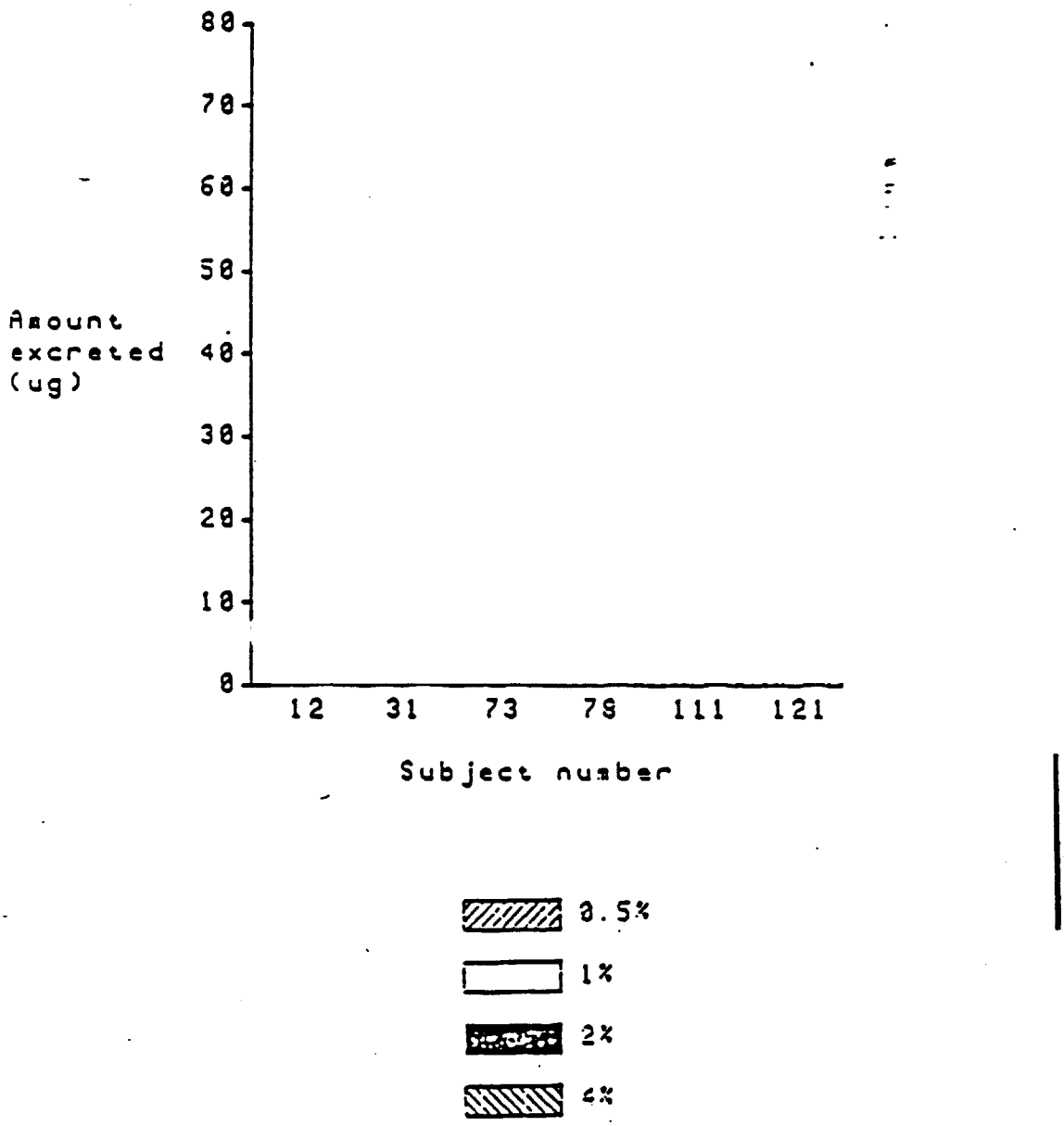

Figure 2 Mean (+/- SEM) urinary excretion of nedocromil sodium in volunteers after administration of different doses to the eye.

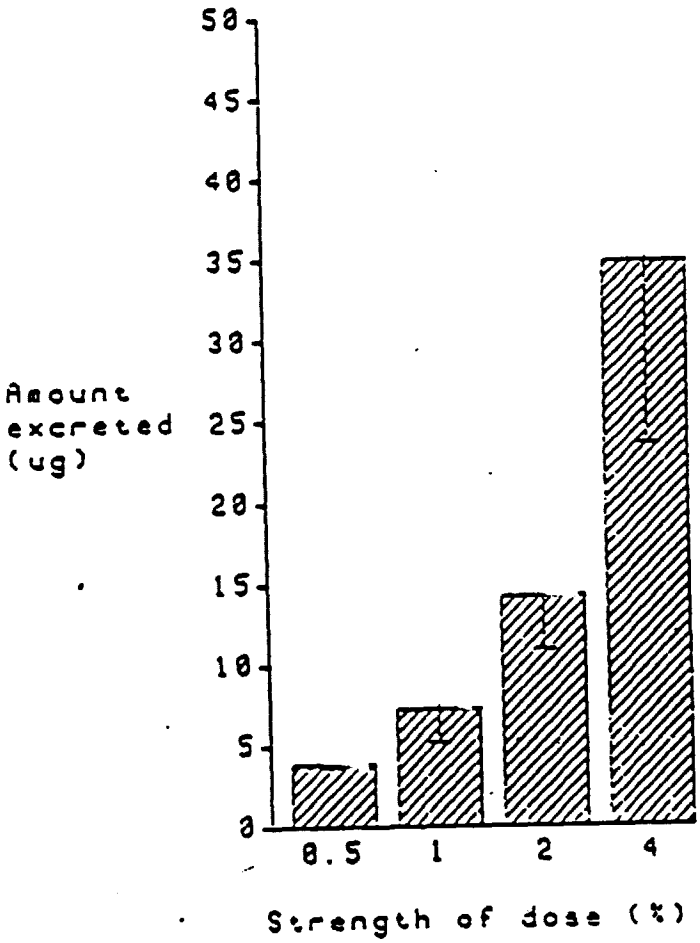

Table 1: Concentrations of [redacted]59002KP in the urine samples

Concantration of [redacted]59002KP administered (%)	Concentration of [redacted]59002KP (ng cm^{-3})					
	Subject number					
	12	31	73	78	111	121
0.5	[redacted]					
1.0						
2.0						
4.0						

STUDY SD 10087/3, CP/HV 219

Table 1: Details of subjects

Subject number	Age (years)	Weight (kg)	Sex (M/F)	Treatment
	30	75	M	1%
	29	61	F	1%
	30	62	F	2%
	27	89	F	2%
	43	68	M	1%
	49	74	M	1%
	48	66	M	1%
	41	68	M	2%
	57	62	F	2%
	43	83	M	2%
	51	69	M	2%
	39	54	F	1%

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